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Henry Ford Health System

Henry Ford Health System Publication List – January 2021

This bibliography aims to recognize the scholarly activity and provide ease of access to journal articles, meeting abstracts, book chapters, books and other works published by Henry Ford Health System personnel. Searches were conducted in PubMed, Embase, and Web of Science during the month, and then imported into EndNote for formatting. There are **117 unique citations** listed this month, with **17 articles on COVID-19**. Articles are listed first, followed by conference abstracts, books and book chapters, and a bibliography of publications on COVID-19. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health System authors.

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Articles

Allergy and Immunology

Turi KN, McKennan C, Gebretsadik T, Snyder B, Seroogy CM, Lemanske RF, Jr., **Zoratti E**, **Havstad S**, Ober C, Lynch S, McCauley K, Yu C, Jackson DJ, Gern JE, and Hartert TV. Unconjugated bilirubin is associated with protection from early-life wheeze and childhood asthma. *J Allergy Clin Immunol* 2021; Epub ahead of print. PMID: 33434532. Full Text

Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.
Department of Statistics, Pittsburgh University, Pittsburgh, PA, USA.
Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA.
Department of Pediatrics, University of Wisconsin, Madison, WI, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA.
Department of Human Genetics, University of Chicago, Chicago, IL, USA.
Division of Gastroenterology, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA.
Department of Pediatrics, University of Wisconsin, Madison, WI, USA. Electronic address: tina.hartert@vumc.org.
Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. Electronic address: gern@medicine.wisc.edu.

BACKGROUND: Wheeze and allergic sensitization are the strongest early-life predictors of childhood asthma development; the molecular origins of these early-life phenotypes are poorly understood. OBJECTIVES: To identify metabolites associated with early-life wheeze, allergic sensitization, and childhood asthma. METHODS: We conducted a nested case-control study using ECHO Program cohorts for discovery and independent replication. Wheeze and allergic sensitization were defined by number of wheeze episodes and positive specific IgE at 1 year of age, respectively. Asthma was defined as physician diagnosis of asthma at age 5 or 6 years. We used untargeted metabolomics, controlling for observed and latent confounding factors, to assess associations between the plasma metabolome and

early-life wheeze, allergy, and childhood asthma. RESULTS: Eighteen plasma metabolites were associated with first year wheeze in the discovery cohort (n=338). Z,Z unconjugated bilirubin (UCB) and its related metabolites exhibited a dose-response relationship with wheeze frequency; UCB levels were 13% (β=0.87, 95%CI=0.74-1.02) and 22% (β=0.78, 95%CI=0.68-0.91) lower in children with 1-3 and 4+ wheeze episodes compared to those who never wheezed, respectively. UCB levels were also associated with childhood asthma (β=0.82, 95%CI=0.68-0.98). Similar trends were observed in two independent cohorts. UCB was significantly negatively correlated with eicosanoid- and oxidative stress-related metabolites. There were no significant associations between metabolites and allergic sensitization. CONCLUSIONS: We identified a novel inverse, dose-dependent association between UCB and recurrent wheeze and childhood asthma. Inflammatory lipid mediators and oxidative stress byproducts inversely correlated with UCB, suggesting UCB modulates pathways critical to the development of early-life recurrent wheeze and childhood asthma.

Anesthesiology

Chauhan G, and **Upadhyay A**. Gadolinium-based contrast agent-induced neurotoxicity: seeing is believing! *BMJ Case Rep* 2021; 14(1). PMID: 33500314. Full Text

Chronic Pain Division, Department of Anesthesiology and Perioperative Medicine, UPMC, Pittsburgh, Pennsylvania, USA CHAUHANG@UPMC.EDU.
Anesthesiology, Pain Management and Perioperative Medicine, Henry Ford Health System, Detroit, Michigan, USA.

Anesthesiology

Fidkowski CW, **Choksi N**, and **Alsaden MR**. A randomized-controlled trial comparing liposomal bupivacaine, plain bupivacaine, and the mixture of liposomal bupivacaine and plain bupivacaine in transversus abdominus plane block for postoperative analgesia for open abdominal hysterectomies. *Can J Anaesth* 2021; Epub ahead of print. PMID: 33432496. Request Article

Department of Anesthesiology, Pain Management, and Perioperative Medicine, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI, 48202, USA. cfidkow1@hfhs.org.
Department of Anesthesiology, Pain Management, and Perioperative Medicine, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI, 48202, USA.

PURPOSE: Transversus abdominus plane (TAP) blocks are widely used for postoperative analgesia for abdominal surgical procedures. The purpose of this study was to compare the analgesic efficacy of plain bupivacaine, liposomal bupivacaine, and the mixture of plain bupivacaine with liposomal bupivacaine when used in a TAP block. METHODS: This study was a single centre, prospective, patient-, observer-, and surgeon-blinded, randomized-controlled trial in which 90 patients undergoing an open abdominal hysterectomy with a midline incision were randomized to receive a TAP block with plain bupivacaine (group bupivacaine), liposomal bupivacaine (group liposomal), or a mixture of liposomal bupivacaine and plain bupivacaine (group mixture). Primary outcomes included time to the first rescue opioid analgesic and total opioid consumption during the first 72 postoperative hours. Secondary outcomes included pain scores, patient satisfaction, incidence of hemodynamic instability, presence of local anesthetic systemic toxicity, and length of hospital stay. RESULTS: The median [interquartile range] time to first opioid was 51 [28-66] min in group bupivacaine, 63 [44-102] min in group liposomal, and 51 [24-84] min in group mixture (P = 0.20). The median [interquartile range] total opioid consumption in the first 72 postoperative hours was 208 [155-270] mg in group bupivacaine, 203 [153-283] mg in group liposomal, and 202 [116-325] mg in group mixture (P = 0.92). There were no significant differences in secondary outcomes between groups. CONCLUSIONS: In this small study at risk of being under-powered, the mixture of liposomal bupivacaine with plain bupivacaine for TAP block did not improve analgesia compared with either liposomal bupivacaine or plain bupivacaine on their own. TRIAL REGISTRATION: www.clinicaltrials.gov (NCT03250507); registered 5 April 2017.

Anesthesiology
Morita Y, Kariya T, **Nagai S**, **Itani A**, **Isley M**, and Tanaka K. Hepatic Vein Flow Index During Orthotopic Liver Transplantation as a Predictive Factor for Postoperative Early Allograft Dysfunction. *J Cardiothorac Vasc Anesth* 2020; Epub ahead of print. PMID: 33455886. Full Text

Department of Anesthesiology, University of Maryland, Baltimore, MD. Electronic address: ymorita@som.umaryland.edu.
Department of Anesthesiology, University of Tokyo, Tokyo, Japan.
Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI.
Department of Anesthesiology, Henry Ford Hospital, Detroit, MI.
Department of Anesthesiology, University of Maryland, Baltimore, MD.

OBJECTIVES: The authors devised a hepatic vein flow index (HVFi), using intraoperative transesophageal echocardiography and graft weight, and investigated its predictive value for postoperative graft function in orthotopic liver transplant. DESIGN: Prospective clinical trial. SETTING, Single-center tertiary academic hospital. PARTICIPANTS: Ninety-seven patients who had orthotopic liver transplant with the piggy-back technique between February 2018 and December 2019. MEASUREMENTS AND MAIN RESULTS: HVFi was defined with HV flow/graft weight. Patients who developed early graft dysfunction (EAD) had low HVFi in systole (HVFi sys, 1.23 v 2.19 L/min/kg, $p < 0.01$), low HVFi in diastole (HVFi dia, 0.87 v 1.54 L/min/kg, $p < 0.01$), low hepatic vein flow (HVF) in systole (HVF sys, 2.04 v 3.95 L/min, $p < 0.01$), and low HVF in diastole (HVF dia, 1.44 v 2.63 L/min, $p < 0.01$). More cardiac death, more vasopressors at the time of measurement, more acute rejection, longer time to normalize total bilirubin (TIME t-bil), longer surgery time, longer neohepatic time, and more packed red blood cell transfusion were observed in the EAD patients. All HVF parameters were negatively correlated with TIME t-bil (HVFi sys $R = -0.406$, $p < 0.01$; HFVi dia $R = -0.442$, $p < 0.01$; HVF sys $R = -0.44$, $p < 0.01$; HVF dia $R = -0.467$, $p < 0.01$). The receiver operating characteristic curve analysis determined the best cut-off levels of HVFi to predict occurrence of EAD (HVFi sys <1.608, HVFi dia <0.784 L/min/kg), acute rejection (HVFi sys <1.388, HVFi dia <1.077 L/min/kg), and prolonged high total bilirubin (HVFi sys <1.471, HVFi dia <1.087 L/min/kg). CONCLUSIONS: The authors' devised HVFi has the potential to predict the postoperative graft function.

Anesthesiology
Sanders JA, **Vaidyanathan A**, **Sayeed H**, **Sherdiwala B**, **Han X**, **Wyman J**, **Wang DD**, and **O'Neill W**. Comparison of Deep Sedation and General Anesthesia With an Endotracheal Tube for Transcaval Transcatheter Aortic Valve Replacement: A Pioneering Institution's Experience. *J Cardiothorac Vasc Anesth* 2021; Epub ahead of print. PMID: 33441271. Full Text

Department of Anesthesiology, Henry Ford Hospital, Detroit, MI. Electronic address: Jsande11@hfhs.org.
Department of Anesthesiology, Henry Ford Hospital, Detroit, MI.
Department of Statistics, Henry Ford Hospital, Detroit, MI.
Department of Cardiology, Henry Ford Hospital, Detroit, MI.

OBJECTIVES: Transcaval transcatheter aortic valve replacement (TC-TAVR) is an alternative approach to transcatheter aortic valve replacement involving deployment of the bioprosthetic valve via a conduit created from the inferior vena cava to the descending aorta in patients for whom the traditional transfemoral approach is not feasible. By analyzing the largest known cohort of TC-TAVR patients, the authors wished to compare hospital length of stay and post-procedure outcomes between patients who underwent the procedure under deep sedation (DS) and patients who underwent general anesthesia with an endotracheal tube. DESIGN: Retrospective, single-center study. SETTING: Henry Ford Hospital in Detroit, MI. PARTICIPANTS: Patients undergoing TC-TAVR from 2015 to 2018. MEASUREMENTS AND MAIN RESULTS: Seventy-nine patients were included in the analysis, which consisted of 38 under general anesthesia with an endotracheal tube and 41 under DS. The sample was divided into a general anesthesia (GA) group and DS group. There were no significant differences in implant success rate or post-procedure outcomes, including in-hospital mortality ($p = 0.999$) and major vascular complication rate ($p = 0.481$), between the two groups. Patients in the GA group stayed a median of 24 hours longer in the intensive care unit (ICU) ($p < 0.001$) and one day longer in the hospital ($p = 0.046$) after the procedure

compared to patients in the DS group. The median procedure time was significantly lower (135 minutes) in the DS group compared to the GA group (167 minutes, p < 0.001). CONCLUSIONS: Patients undergoing TC-TAVR under DS had similar postoperative outcomes and shorter post-procedure hospital and ICU lengths of stay compared to general anesthesia. In the authors' experience, DS is the preferred anesthetic technique for TC-TAVR.

Cardiology/Cardiovascular Research

Allen BR, Christenson RH, Cohen SA, **Nowak R**, Wilkerson RG, Mumma B, Madsen T, **McCord J**, Huis In't Veld M, Massoomi M, Stopyra JP, Montero C, Weaver MT, Yang K, and Mahler SA. Diagnostic Performance of High Sensitivity Cardiac Troponin T Strategies and Clinical Variables in a Multisite United States Cohort. *Circulation* 2021; Epub ahead of print. PMID: 33474976. Full Text

Department of Emergency Medicine, College of Medicine, University of Florida, Gainesville, FL.
Department of Pathology, University of Maryland School of Medicine, Baltimore, MD.
Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI.
Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD.
Department of Emergency Medicine, School of Medicine, University of California Davis, Sacramento, CA.
Division of Emergency Medicine, University of Utah School of Medicine, Salt Lake City, UT.
Heart and Vascular Institute and Department of Internal Medicine Henry Ford Hospital, Detroit, MI.
Division of Cardiology, Department of Internal Medicine, College of Medicine, University of Florida, Gainesville, FL.
Department of Emergency Medicine, Wake Forest School of Medicine, Winston-Salem, NC.
Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, FL.
Department of Biostatistics, College of Public Health and Health Professions, University of Florida, Gainesville, FL.

Background: European data support the use of low high-sensitivity troponin (hs-cTn) measurements or a 0/1-hour (0/1-h) algorithm for myocardial infarction (MI) or to exclude major adverse cardiac events (MACE) among Emergency Department (ED) patients with possible acute coronary syndrome (ACS). However, modest US data exist to validate these strategies. This study evaluated the diagnostic performance of an initial hs-cTnT measure below the limit of quantification (LOQ: 6 ng/L), a 0/1-h algorithm, and their combination with HEART scores for excluding MACE in a multisite US cohort. Methods: A prospective cohort study was conducted at 8 US sites, enrolling adult ED patients with symptoms suggestive of ACS and without ST-elevation on electrocardiogram. Baseline and 1-hour blood samples were collected and hs-cTnT (Roche, Basel Switzerland) measured. Treating providers blinded to hs-cTnT results prospectively calculated HEART scores. MACE (cardiac death, MI, and coronary revascularization) at 30-days was adjudicated. The proportion of patients with initial hs-cTnT measures <LOQ and risk based on a 0/1-h algorithm was determined. The negative predictive value (NPV) was calculated for both strategies when used alone or with a HEART score. Results: Among 1,462 participants with initial hs-cTnT measures, 46.4% (678/1,462) were women and 37.1% (542/1,462) were African American with a mean age of 57.6 (SD±12.9) years. MACE at 30-days occurred in 14.4% (210/1,462). Initial hs-cTnT measures <LOQ occurred in 32.8% (479/1,462), yielding a NPV of 98.3% (95%CI: 96.7-99.3%) for 30-day MACE. A low risk HEART score with an initial hs-cTnT < LOQ occurred in 20.1% (294/1,462) yielding a NPV of 99.0% (95%CI: 97.0-99.8%) for 30-day MACE. A 0/1-h algorithm was complete in 1,430 patients, ruling-out 57.8% (826/1,430) with a NPV of 97.2% (95%CI: 95.9-98.2%) for 30-day MACE. Adding a low HEART score to the 0/1-h algorithm ruled-out 30.8% (441/1430) with a NPV of 98.4% (95%CI: 96.8-99.4%) for 30-day MACE. Conclusions: In a prospective multisite US cohort, an initial hs-cTnT <LOQ combined with a low risk HEART score has 99% NPV for 30-day MACE. The 0/1-h hs-cTnT algorithm did not achieve a NPV > 99% for 30-day MACE when used alone or with a HEART score. Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT02984436.

Cardiology/Cardiovascular Research

Brawner CA, **Ehrman JK**, **Bole S**, **Kerrigan DJ**, **Parikh SS**, **Lewis BK**, **Gindi RM**, **Keteyian C**, **Abdul-Nour K**, and **Keteyian SJ**. Inverse Relationship of Maximal Exercise Capacity to Hospitalization Secondary to Coronavirus Disease 2019. *Mayo Clin Proc* 2021; 96(1):32-39. PMID: 33413833. Full Text

Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI. Electronic address: cbrawne1@hfhs.org.
Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI.
Public Health Sciences, Henry Ford Health System, Detroit, MI.
Population Health, Henry Ford Allegiance Health, Jackson, MI.

OBJECTIVE: To investigate the relationship between maximal exercise capacity measured before severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and hospitalization due to coronavirus disease 2019 (COVID-19). METHODS: We identified patients (≥18 years) who completed a clinically indicated exercise stress test between January 1, 2016, and February 29, 2020, and had a test for SARS-CoV-2 (ie, real-time reverse transcriptase polymerase chain reaction test) between February 29, 2020, and May 30, 2020. Maximal exercise capacity was quantified in metabolic equivalents of task (METs). Logistic regression was used to evaluate the likelihood that hospitalization secondary to COVID-19 is related to peak METs, with adjustment for 13 covariates previously identified as associated with higher risk for severe illness from COVID-19. RESULTS: We identified 246 patients (age, 59±12 years; 42% male; 75% black race) who had an exercise test and tested positive for SARS-CoV-2. Among these, 89 (36%) were hospitalized. Peak METs were significantly lower (P<.001) among patients who were hospitalized (6.7±2.8) compared with those not hospitalized (8.0±2.4). Peak METs were inversely associated with the likelihood of hospitalization in unadjusted (odds ratio, 0.83; 95% CI, 0.74-0.92) and adjusted models (odds ratio, 0.87; 95% CI, 0.76-0.99). CONCLUSION: Maximal exercise capacity is independently and inversely associated with the likelihood of hospitalization due to COVID-19. These data further support the important relationship between cardiorespiratory fitness and health outcomes. Future studies are needed to determine whether improving maximal exercise capacity is associated with lower risk of complications due to viral infections, such as COVID-19.

Cardiology/Cardiovascular Research

Gheorghe LL, Mobasseri S, Agricola E, **Wang DD**, Milla F, Swaans M, Pandis D, Adams DH, Yadav P, Sievert H, Ailawadi G, and Sorajja P. Imaging for Native Mitral Valve Surgical and Transcatheter Interventions. *JACC Cardiovasc Imaging* 2021; 14(1):112-127. PMID: 33413881. Full Text

Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands; Department of Cardiology, Puerta del Mar Hospital, Cadiz, Spain. Electronic address: livia_gheorghe_ro@yahoo.es.
Marcus Heart Valve Center, Piedmont Heart Institute, Atlanta, Georgia, USA.
School of Medicine, Cardio-Thoracic Vascular Department, Vita-Salute San Raffaele University, Milan, Italy, and Cardiovascular Imaging Unit, Cardio-Thoracic-Vascular Department, IRCCS San Raffaele Scientific Institute, Milan, Italy.
Division of Cardiology, Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan, USA.
Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands.
Department of Cardiovascular Surgery, Icahn School of Medicine at Mount Sinai, New York, New York, USA.
CardioVascular Center Frankfurt, Frankfurt, Germany, Anglia Ruskin University, Chelmsford, United Kingdom; University of California San Francisco, San Francisco, California; Yunnan Hospital Fuwai, Kunming, China.
Division of Thoracic and Cardiovascular Surgery, Department of Surgery, University of Virginia, Charlottesville, Virginia, USA.
Valve Science Center, Minneapolis Heart Institute Foundation, Abbott Northwestern Hospital, Minneapolis, Minnesota, USA.

There has been rapid progress in transcatheter therapies for mitral regurgitation. These developments have elevated the need for the imager to have a core understanding of the functional mitral valve anatomy. Pre- and intraoperative echocardiography for surgical mitral valve repair for mitral regurgitation has defined contemporary interventional imaging in many ways. The central tenets of these principles apply to interventional imaging of transcatheter mitral valve interventions. However, the heightened emphasis on procedural planning and procedural imaging is one of the new challenges posed by transcatheter interventions. This need for accurate and reliable information has required the imager to be

agnostic to the imaging modality. Cardiac computed tomography has become critical in procedural planning in this new paradigm. The expanded use of pre-procedural cardiac magnetic resonance to quantify mitral regurgitation and characterize the left ventricle is another illustration of this newer approach. Other illustrations of the new world of interventional imaging include the expanded use of 3-dimensional (3D) transesophageal echocardiography and real-time fusion of echocardiography and fluoroscopy images. Imaging data are also the basis for computational modeling, 3D printing, and artificial intelligence. These technologies are being increasingly explored to improve therapy selection and prediction of procedural outcomes. This review provides an update of the essentials in present interventional imaging for surgical and transcatheter interventions for mitral regurgitation.

Cardiology/Cardiovascular Research
Greenberg JC, **Altawil MR**, and **Singh G**. Life Saving Therapy Inhibition by Phones Containing Magnets. *Heart Rhythm* 2021; Epub ahead of print. PMID: 33418126. Full Text

Section of Cardiac Electrophysiology, Henry Ford Heart and Vascular Institute, Henry Ford Hospital 2799 West Grand Boulevard, Detroit, Michigan, 48202.

Cardiology/Cardiovascular Research
Karacsonyi J, Stanberry L, **Alaswad K**, Krestyaninov O, Choi JW, Rangan BV, Nikolakopoulos I, Vemmou E, Ungi I, and Brilakis ES. Predicting Technical Success of Chronic Total Occlusion Percutaneous Coronary Intervention: Comparison of 3 Scores. *Circ Cardiovasc Interv* 2021; 14(1):e009860. PMID: 33423537. Full Text

Minneapolis Heart Institute and Minneapolis Heart Heart Institute Foundation, Abbott Northwestern Hospital, MN (J.K., L.S., B.V.R., I.N., E.V., E.S.B.).
Division of Invasive Cardiology, Second Department of Internal Medicine and Cardiology Center, University of Szeged, Hungary (J.K., I.U.).
Henry Ford Hospital, Detroit, MI (K.A.).
Meshalkin Novosibirsk Research Institute, Russia (O.K.).
Baylor Heart and Vascular Hospital, Dallas, TX (J.W.C.).

Cardiology/Cardiovascular Research
Keteyian SJ, **Grimshaw C**, **Brawner CA**, **Kerrigan DJ**, **Reasons L**, **Berry R**, **Peterson EL**, and **Ehrman JK**. A Comparison of Exercise Intensity in Hybrid Versus Standard Phase Two Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev* 2021; 41(1):19-22. PMID: 33351540. Full Text

Division of Cardiovascular Medicine (Drs Keteyian, Brawner, Kerrigan, and Ehrman, Ms Grimshaw and Reasons, and Mr Berry) and Department of Public Health Sciences (Dr Peterson), Henry Ford Health System, Detroit, Michigan.

PURPOSE: To compare exercise training intensity during standard cardiac rehabilitation (S-CR) versus hybrid-CR (combined clinic- and remote home-/community-based). METHODS: The iATTEND (improving ATTENDance to cardiac rehabilitation) trial is currently enrolling subjects and randomizing patients to S-CR versus hybrid-CR. This substudy involves the first 47 subjects who completed ≥18 CR sessions. Patients in S-CR completed all visits in a typical phase II clinic-based setting and patients in hybrid-CR completed up to 17 of their sessions remotely using telehealth (TH). Exercise training intensity in both CR settings is based on heart rate (HR) data from each CR session, expressed as percent HR reserve. RESULTS: Among patients in both study groups, there were no serious adverse events or falls that required hospitalization during or within 3 hr after completing a CR session. Expressed as a percentage of HR reserve, the overall mean exercise training intensities during both the S-CR sessions and the TH-CR sessions from hybrid-CR were not significantly different at 63 ± 12% and 65 ± 10%, respectively (P = .29). CONCLUSION: This study showed that hybrid-CR delivered using remote TH results in exercise training intensities that are not significantly different from S-CR.

Cardiology/Cardiovascular Research

Lemor A, **Al-Darzi W**, **O'Neill W**, and **Basir MB**. Unmasking right ventricular failure in cardiogenic shock: The importance of serial hemodynamics. *Catheter Cardiovasc Interv* 2021; Epub ahead of print. PMID: 33484043. Full Text

Department of Cardiology, Henry Ford Hospital, Detroit, Michigan.
Universidad de San Martín de Porres, Facultad de Medicina, Centro de Investigación de Epidemiología Clínica y Medicina Basada en la Evidencia Lima, Peru.

A 65-year-old female was transferred with myocardial infarction, three-vessel coronary artery disease, cardiogenic shock and an intraaortic balloon pump. Given persistent shock, mechanical circulatory support (MCS) was upgraded using a left ventricular hemodynamic support device (Impella CP). The patient was monitored in the catheterization laboratory and serial hemodynamic measures were obtained. Initial hemodynamics showed relative improvement; however, serial assessments demonstrated worsening hemodynamics secondary to right ventricular failure, ultimately requiring a right ventricular hemodynamic support device. The case highlights the rapid changes that can occur with mechanical circulatory support devices and demonstrates the importance of obtaining serial hemodynamics in the cardiac catheterization laboratory.

Cardiology/Cardiovascular Research

Maskoun W, Abualsuod A, Habash F, Madmani ME, Khaled K, Gheith Z, Alqam B, Miller JM, and Vallurupalli S. Cryoballoon vs radiofrequency ablation of atrial fibrillation: insights from the Veterans Healthcare System. *J Interv Card Electrophysiol* 2021; Epub ahead of print. PMID: 33415707. Full Text

Section of Electrophysiology, Division of Cardiology, Department of Internal Medicine, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI, 48202, USA. wmaskou1@hfhs.org.
Indiana University Health System, Indianapolis, IN, USA.
University of Arkansas for Medical Sciences, Little Rock, AR, USA.
Central of Arkansas Veterans Healthcare system, Little Rock, AR, USA.
Louisiana State University Shreveport, Shreveport, LA, USA.
University of Kansas Medical Center, Kansas City, KS, USA.
Presbyterian Hospital, Albuquerque, NM, USA.

PURPOSE: Catheter ablation is considered the mainstay treatment for drug-refractory atrial fibrillation (AF). The aims of our study were to compare the efficacy and safety of the most two currently approved approaches (point-by-point radiofrequency ablation (RFA), either with contact force (CF) or without contact force (nCF) catheters, and cryoballoon ablation (CBA)) in the Veterans Healthcare System. METHODS: We performed a retrospective study of patients who underwent ablation for treatment of AF at the veterans affairs healthcare system between 2013 and 2018. Only the first reported ablation procedure was included. RESULTS: We included 956 patients in the study (97.4% males, 91.5% Caucasians, 67% paroxysmal AF), with 682 patients in RFA-nCF, 139 in RFA-CF, and 135 in CBA. Thirty-day complication rates were comparable between the three groups with the exception of higher incidence of phrenic nerve injury in CBA group when compared to RFA-nCF (2.2% vs 0.0%, $p < 0.01$). Long-term recurrence rate of AF was significantly lower in the CBA group when compared to RFA-nCF (33.3% vs 47.7%, adjusted HR 0.60, 95% CI 0.44-0.83, $p < 0.01$). On the other hand, it was similar between RFA-CF and RFA-nCF groups (43.9% vs 47.7%, adjusted HR 1.01, 95% CI 0.76-1.33, p 0.97). After stratifying patients based on AF type, these findings were only present in patients with paroxysmal AF. CONCLUSION: CBA for paroxysmal AF, in male dominant patients' population, was associated with lower incidence of AF recurrence rate while having a comparable safety profile to RFA independent of the use of CF catheters.

Cardiology/Cardiovascular Research

Mishra K, **Naffouj S**, **Gorgis S**, **Ibrahim H**, **Gill S**, **Fadel R**, **Chatfield A**, **Tang A**, and **Salgia R**. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. *Hepatol Commun* 2021; 5(1):24-32. PMID: 33437898. Full Text

Department of Internal Medicine Henry Ford Hospital Detroit MI USA.
Division of Cardiology Department of Medicine Henry Ford Hospital Detroit MI USA.
Department of Public Health Sciences Henry Ford Hospital Detroit MI USA.
Division of Gastroenterology and Hepatology Department of Medicine Henry Ford Hospital Detroit MI USA.

Respiratory failure is the most common cause of death in patients with corona virus disease 2019 (COVID-19). There have been many investigations to determine predictors of bad outcomes in patients with this illness. Liver enzyme elevation has been described in hospitalized patients with severe COVID-19; however, little is known about the significance of liver injury regarding outcomes. We conducted a retrospective chart review of 348 patients admitted with COVID-19 in our quaternary care center. Liver injury on admission was defined based on the laboratory cutoff of aspartate aminotransferase >35 IU/L and/or alanine aminotransferase >52 IU/L. Patients were divided into two cohorts based on the presence or absence of liver injury. These cohorts were compared to assess differences in presentation, complications, and outcomes. The primary outcome was respiratory failure requiring intubation, and the secondary outcome was in-hospital mortality. The presence of new onset liver enzyme elevation on presentation was associated with increased severity of illness, need for mechanical ventilation, and mortality. Presence of liver injury increased the chance of acute hypoxic respiratory failure requiring mechanical ventilation by 1.79 times. The degree and timeline of liver enzyme elevation during hospitalization corresponded with elevations of other inflammatory markers. Conclusion: Liver injury appears to correlate with the inflammatory syndrome caused by COVID-19, with the degree of liver injury corresponding with severity of inflammation. We suggest early and continued monitoring of liver enzymes as they can be useful to identify patients who may need early escalation of care.

Cardiology/Cardiovascular Research

Molina EJ, Shah P, Kiernan MS, Cornwell WK, 3rd, Copeland H, Takeda K, Fernandez FG, Badhwar V, Habib RH, Jacobs JP, Koehl D, Kirklin JK, Pagani FD, and **Cowger JA**. The Society of Thoracic Surgeons Intermacs 2020 Annual Report. *Ann Thorac Surg* 2021; Epub ahead of print. PMID: 33465365. Full Text

Department of Cardiac Surgery, MedStar Heart & Vascular Institute, Georgetown University, Washington, DC.
Department of Heart Failure and Transplantation, Inova Heart and Vascular Institute, Falls Church, VA.
Cardiovascular Center, Division of Cardiology, Tufts Medical Center, Boston, MA.
Department of Medicine-Cardiology, University of Colorado Anschutz Medical Campus, Aurora, CO.
Division of Cardiothoracic and Vascular Surgery, Lutheran Hospital, Indiana University School of Medicine, Fort Wayne, IN.
Division of Cardiothoracic Surgery, Department of Surgery, Columbia University, New York, NY.
Division of Cardiothoracic Surgery, Department of Surgery, Emory University School of Medicine, Atlanta, GA.
Department of Cardiovascular and Thoracic Surgery, West Virginia University, Morgantown, WV.
STS Research Center, The Society of Thoracic Surgeons, Chicago, IL.
Division of Thoracic and Cardiovascular Surgery, Department of Surgery, University of Florida, Gainesville, FL.
Kirklin Institute for Research in Surgical Outcomes, Birmingham, AL.
Kirklin Institute for Research in Surgical Outcomes, Birmingham, AL; Division of Cardiothoracic Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, AL.
Department of Cardiac Surgery, University of Michigan, Ann Arbor, M.
Henry Ford Hospital, Division of Cardiovascular Medicine, Detroit, MI. Electronic address: jennifercowger@gmail.com.

The STS-Intermacs 2020 Annual Report reviews outcomes on 25,551 patients undergoing primary isolated continuous flow left ventricular assist device (LVAD) implantation between 2010-2019. In 2019, 3,198 primary LVADs were implanted, which is the highest annual volume in Registry history. Compared with the previous era (2010-2014), patients implanted in the most recent era (2015-2019) were more likely to be African American (26.8% vs. 22.9%, P<.0001) and more likely to be bridged to durable LVAD

with temporary mechanical support devices (36.8% vs 26.0%, P<.0001). In 2019, 50% of patients were INTERMACS 1-2 prior to durable LVAD and 73% were implanted as destination therapy. Maglev technology has become the predominant design, accounting for 77% of devices in 2019. The 1- and 2-year survival in the most recent era has improved compared to 2010-2014 (82.3% and 73.1% vs. 80.5% and 69.1%, respectively; P<.0001). Major bleeding and infection continue to be the leading adverse events. Incident stroke has declined in the current era to 12.7% at one-year. STS-Intermacs research publications are highlighted herein and the new quality initiatives are introduced.

Cardiology/Cardiovascular Research

Nowak RM, **Jacobsen G**, Limkakeng A, Jr., Peacock WF, Christenson RH, **McCord J**, Apple FS, Singer AJ, and deFilippi CR. Outpatient versus observation/inpatient management of emergency department patients rapidly ruled-out for acute myocardial infarction: Findings from the HIGH-US study. *Am Heart J* 2021; 231:6-17. PMID: 33127532. Full Text

Department of Emergency Medicine, Henry Ford Health System, Detroit, MI.
Department of Epidemiology and Statistics, Henry Ford Health System, Detroit, MI.
Division of Emergency, Medicine, Duke University School of Medicine, Durham, NC.
Department of Emergency Medicine, Baylor College of Medicine, Houston, TX.
University of Maryland School of Medicine, Baltimore, MD.
Heart and Vascular Institute, Henry Ford Health System, Detroit, MI.
Department of Laboratory Medicine and Pathology, Hennepin County Medical Center of Hennepin Healthcare and University of Minnesota Minneapolis, Minneapolis, MN.
Department of Emergency Medicine, SUNY Stony Brook, Stony Brook, New York, NY.
Inova Heart and Vascular Institute, Falls Church, VA. Electronic address: Christopher.Defilippi@Inova.org.

BACKGROUND: The actual Emergency Department (ED) dispositions of patients enrolled in observational studies and meeting criteria for rapid acute myocardial infarction (AMI) rule-out are unknown. Additionally, their presenting clinical profiles, cardiac testing/treatments received, and outcomes have not been reported. METHODS: Patients in the HIGH-US study (29 sites) that ruled-out for AMI using a high-sensitivity cardiac troponin I 0/1-hour algorithm were evaluated. Clinical characteristics of patients having ED discharge were compared to patients placed in observation or hospital admitted (OBS/ADM). Reports of any OBS/ADM cardiac stress test (CST), cardiac catheterization (Cath) and coronary revascularization were reviewed. One year AMI/death and major adverse cardiovascular event rates were determined. RESULTS: Of the 1,020 ruled-out AMI patients 584 (57.3%) had ED discharge. The remaining 436 (42.7%) were placed in OBS/ADM. Patients with risk factors for AMI, including personal or family history of coronary artery disease, hypertension, previous stroke or abnormal ECG were more often placed in OBS/ADM. 175 (40.1%) had a CST. Of these 32 (18.3%) were abnormal and 143 (81.7%) normal. Cath was done in 11 (34.3%) of those with abnormal and 13 (9.1%) with normal CST. Of those without an initial CST 85 (32.6%) had Cath. Overall, revascularizations were performed in 26 (6.0%) patients. One-year AMI/death rates were low/similar (P = .553) for the groups studied. CONCLUSIONS: Rapidly ruled-out for AMI ED patients having a higher clinician perceived risk for new or worsening coronary artery disease and placed in OBS/ADM underwent many diagnostic tests, were infrequently revascularized and had excellent outcomes. Alternate efficient strategies for these patients are needed.

Cardiology/Cardiovascular Research

Panagides V, Vase H, Shah SP, **Basir MB**, Mancini J, Kamran H, Batra S, Laine M, Eiskjær H, Christensen S, Karami M, Paganelli F, Henriques JPS, and Bonello L. Impella CP Implantation during Cardiopulmonary Resuscitation for Cardiac Arrest: A Multicenter Experience. *J Clin Med* 2021; 10(2). PMID: 33477532. Full Text

Intensive Care Unit, Department of Cardiology, Assistance Publique-Hôpitaux de Marseille, Hôpital Nord, Aix-Marseille University, 13015 Marseille, France.
Mediterranean Association for Research and Studies in Cardiology (MARS Cardio), 13015 Marseille, France.

Centre for CardioVascular and Nutrition Research (C2VN), INSERM 1263, INRA 1260, 13015 Marseille, France.
Department of Cardiology, Aarhus University Hospital, 8200 Aarhus, Denmark.
Department of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, MA 01805, USA.
Department of Cardiology, Henry Ford Hospital, Detroit, MI 48202, USA.
Department of Public Health (BIOSTIC), Aix-Marseille University, INSERM, IRD, APHM, UMR1252, SESSTIM, Hôpital de la Timone, 13005 Marseille, France.
Department of Intensive Care Medicine, Aarhus University Hospital, 8200 Aarhus, Denmark.
Department of Cardiology, Heart Center, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, 1081 HV Amsterdam, The Netherlands.

BACKGROUND: Impella CP is a left ventricular pump which may serve as a circulatory support during cardiopulmonary resuscitation (CPR) for cardiac arrest (CA). Nevertheless, the survival rate and factors associated with survival in patients undergoing Impella insertion during CPR for CA are unknown. METHODS: We performed a retrospective multicenter international registry of patients undergoing Impella insertion during on-going CPR for in- or out-of-hospital CA. We recorded immediate and 30-day survival with and without neurologic impairment using the cerebral performance category score and evaluated the factors associated with survival. RESULTS: Thirty-five patients had an Impella CP implanted during CPR for CA. Refractory ventricular arrhythmias were the most frequent initial rhythm (65.7%). In total, 65.7% of patients immediately survived. At 30 days, 45.7% of patients were still alive. The 30-day survival rate without neurological impairment was 37.1%. In univariate analysis, survival was associated with both an age < 75 years and a time from arrest to CPR ≤ 5 min ($p = 0.035$ and $p = 0.008$, respectively). CONCLUSIONS: In our multicenter registry, Impella CP insertion during ongoing CPR for CA was associated with a 37.1% rate of 30-day survival without neurological impairment. The factors associated with survival were a young age and a time from arrest to CPR ≤ 5 min.

Cardiology/Cardiovascular Research
Qintar M, **Wang DD**, **O'Neill WW**, and **O'Neill B**. Non-coaptation of an implanted caval valve leaflets for severe tricuspid regurgitation: Rethinking the concept of "Eustachian ridge?". *Catheter Cardiovasc Interv* 2021; Epub ahead of print. PMID: 33491842. Full Text

Center for Structural Heart Disease, Division of Cardiology, Henry Ford Health System, Detroit, Michigan, USA.

Severe symptomatic tricuspid regurgitation (TR) remains an undertreated disease. Multiple trans-catheter treatment options are currently under investigation. Transcatheter caval valve implantation (CAVI) has been utilized as a treatment option and aims at decreasing or eliminating the caval backflow that occurs in severe TR patients. Understanding challenges with this therapy is paramount. Hereby we present a CAVI case with resultant non-coaptation of valve leaflets in a patient with a prominent Eustachian ridge.

Cardiology/Cardiovascular Research
Raad M, **Gorgis S**, **Dabbagh M**, Chehab O, **Parikh S**, and **Singh G**. Right Heart Strain on Presenting 12-Lead Electrocardiogram Predicts Critical Illness in COVID-19. *JACC Clin Electrophysiol* 2020; Epub ahead of print. PMID: 33358667. Full Text

Division of Cardiology, Department of Medicine, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Medicine, Wayne State University-Detroit Medical Center, Detroit, Michigan, USA.
Section of Cardiac Electrophysiology, Department of Medicine, Henry Ford Hospital, Detroit, Michigan, USA. Electronic address: Gsingh1@hfhs.org.

OBJECTIVES: This study aimed to assess the association of new right heart strain patterns on presenting 12-lead electrocardiogram (RHS-ECG) with outcomes in patients hospitalized with COVID-19. BACKGROUND: Cardiovascular comorbidities and complications, including right ventricular dysfunction, are common and are associated with worse outcomes in patients with COVID-19. The data on the clinical usefulness of the 12-lead ECG to aid with prognosis are limited. METHODS: This study retrospectively evaluated records from 480 patients who were consecutively admitted with COVID-19. ECGs obtained at

presentation in the emergency department (ED) were considered index ECGs. RHS-ECG was defined by any new right-axis deviation, S(1)Q(3)T(3) pattern, or ST depressions with T-wave inversions in leads V(1) to V(3) or leads II, III, and aVF. Multivariable logistic regression was performed to assess whether RHS-ECGs were independently associated with primary outcomes. RESULTS: ECGs from the ED were available for 314 patients who were included in the analysis. Most patients were in sinus rhythm, with sinus tachycardia being the most frequent dysrhythmia. RHS-ECG findings were present in 40 (11%) patients. RHS-ECGs were significantly associated with the incidence of adverse outcomes and an independent predictor of mortality (adjusted odds ratio [adjOR]: 15.2; 95% confidence interval [CI]: 5.1 to 45.2; $p < 0.001$), the need for mechanical ventilation (adjOR: 8.8; 95% CI: 3.4 to 23.2; $p < 0.001$), and their composite (adjOR: 12.1; 95% CI: 4.3 to 33.9]; $p < 0.001$). CONCLUSIONS: RHS-ECG was associated with mechanical ventilation and mortality in patients admitted with COVID-19. Special attention should be taken in patients admitted with new signs of RHS on presenting ECG.

Cardiology/Cardiovascular Research

Rachwan RJ, Kutkut I, Timsina LR, Bou Chaaya RG, El-Am EA, Sabra M, **Mshelbwala FS**, Rahal MA, Lacerda MA, Kubal CA, Fridell JA, Ghabril MS, Bourdillon PD, and Mangus RS. CAD-LT score effectively predicts risk of significant coronary artery disease in liver transplant candidates. *J Hepatol* 2021; Epub ahead of print. PMID: 33476745. Full Text

Division of Cardiovascular Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA.
Division of Cardiology, NewYork-Presbyterian Brooklyn Methodist Hospital, Brooklyn, New York, USA.
Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana, USA.
Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA.
Division of Cardiology, Henry Ford Hospital, Detroit, Michigan, USA.
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA.
Department of Transplantation Surgery, Indiana University School of Medicine, Indianapolis, Indiana, USA.
Division of Cardiology, Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA.
Department of Transplantation Surgery, Indiana University School of Medicine, Indianapolis, Indiana, USA. Electronic address: rmangus@iupui.edu.

BACKGROUND AND AIMS: Patients with cirrhosis and significant coronary artery disease (CAD) are at risk for peri-liver transplantation (LT) cardiac events. The Coronary Artery Disease in Liver Transplantation (CAD-LT) score and algorithm aim to predict the risk of significant CAD in LT candidates and guide pre-LT cardiac evaluation. METHODS: Patients who underwent pre-LT evaluation at Indiana University (2010-2019) were studied retrospectively. Stress echocardiography (SE) and cardiac catheterization (CATH) reports were reviewed. CATH was performed for predefined CAD risk factors, irrespective of normal SE. Significant CAD was defined as CAD requiring percutaneous or surgical intervention. A multivariate regression model was constructed to assess risk factors. Receiver Operating Curve analysis was used to compute a point-based risk score and a stratified testing algorithm. RESULTS: A total of 1771 pre-LT patients underwent cardiac evaluation, including results from 1634 SE and 1266 CATH. Risk-adjusted predictors of significant CAD at CATH were older age (adjusted odds ratio 1.05 [95% confidence interval 1.03-1.08]), male gender (1.69 [1.16-2.50]), diabetes (1.57 [1.12-2.22]), hypertension (1.61 [1.14-2.28]), tobacco use (pack years) (1.01 [1.00-1.02]), family history of CAD (1.63 [1.16-2.28]), and personal history of CAD (6.55 [4.33-9.90]). The CAD-LT score stratified significant CAD risk as low (≤2%), intermediate (3% to 9%), and high (≥10%). Among patients who underwent CATH, a risk-based testing algorithm (Low: no testing; Intermediate: non-invasive testing vs. CATH; High: CATH) would have identified 97% of all significant CAD and potentially avoided unnecessary testing (669 SE [57%] and 561 CATH [44%]). CONCLUSIONS: The CAD-LT score and algorithm (available at www.cad-lt.com) effectively stratify pre-LT risk for significant CAD. This may inform more targeted testing of candidates with fewer tests and faster time to waitlist.

Cardiology/Cardiovascular Research

Sadiq O, **Simmer S**, **Watson A**, **Eng M**, **Frisoli T**, and **Zuchelli T**. Colovaginal fistula closure using a cardiac septal defect occluder. *VideoGIE* 2021; 6(1):41-43. PMID: 33490756. Full Text

Division of Gastroenterology, Henry Ford Hospital, Detroit, Michigan.
Division of Cardiology, Henry Ford Hospital, Detroit, Michigan.

Cardiology/Cardiovascular Research

Sanders JA, **Vaidyanathan A**, **Sayeed H**, **Sherdiwala B**, **Han X**, **Wyman J**, **Wang DD**, and **O'Neill W**. Comparison of Deep Sedation and General Anesthesia With an Endotracheal Tube for Transcaval Transcatheter Aortic Valve Replacement: A Pioneering Institution's Experience. *J Cardiothorac Vasc Anesth* 2021; Epub ahead of print. PMID: 33441271. Full Text

Department of Anesthesiology, Henry Ford Hospital, Detroit, MI. Electronic address: Jsande11@hfhs.org.
Department of Anesthesiology, Henry Ford Hospital, Detroit, MI.
Department of Statistics, Henry Ford Hospital, Detroit, MI.
Department of Cardiology, Henry Ford Hospital, Detroit, MI.

OBJECTIVES: Transcaval transcatheter aortic valve replacement (TC-TAVR) is an alternative approach to transcatheter aortic valve replacement involving deployment of the bioprosthetic valve via a conduit created from the inferior vena cava to the descending aorta in patients for whom the traditional transfemoral approach is not feasible. By analyzing the largest known cohort of TC-TAVR patients, the authors wished to compare hospital length of stay and post-procedure outcomes between patients who underwent the procedure under deep sedation (DS) and patients who underwent general anesthesia with an endotracheal tube. DESIGN: Retrospective, single-center study. SETTING: Henry Ford Hospital in Detroit, MI. PARTICIPANTS: Patients undergoing TC-TAVR from 2015 to 2018. MEASUREMENTS AND MAIN RESULTS: Seventy-nine patients were included in the analysis, which consisted of 38 under general anesthesia with an endotracheal tube and 41 under DS. The sample was divided into a general anesthesia (GA) group and DS group. There were no significant differences in implant success rate or post-procedure outcomes, including in-hospital mortality ($p = 0.999$) and major vascular complication rate ($p = 0.481$), between the two groups. Patients in the GA group stayed a median of 24 hours longer in the intensive care unit (ICU) ($p < 0.001$) and one day longer in the hospital ($p = 0.046$) after the procedure compared to patients in the DS group. The median procedure time was significantly lower (135 minutes) in the DS group compared to the GA group (167 minutes, $p < 0.001$). CONCLUSIONS: Patients undergoing TC-TAVR under DS had similar postoperative outcomes and shorter post-procedure hospital and ICU lengths of stay compared to general anesthesia. In the authors' experience, DS is the preferred anesthetic technique for TC-TAVR.

Cardiology/Cardiovascular Research

Wang DD, Qian Z, Vukicevic M, Engelhardt S, Kheradvar A, Zhang C, Little SH, Verjans J, Comaniciu D, **O'Neill WW**, and Vannan MA. 3D Printing, Computational Modeling, and Artificial Intelligence for Structural Heart Disease. *JACC Cardiovasc Imaging* 2021; 14(1):41-60. PMID: 32861647. Full Text

Center for Structural Heart Disease, Division of Cardiology, Henry Ford Health System, Detroit, Michigan, USA. Electronic address: dwang2@hfhs.org.
Hippocrates Research Lab, Tencent America, Palo Alto, California, USA.
Department of Cardiology, Methodist DeBakey Heart Center, Houston Methodist Hospital, Houston, Texas, USA.
Artificial Intelligence in Cardiovascular Medicine, Heidelberg University Hospital, Heidelberg, Germany.
Department of Biomedical Engineering, Edwards Lifesciences Center for Advanced Cardiovascular Technology, University of California, Irvine, California, USA.
H. Milton Stewart School of Industrial & Systems Engineering and Georgia Tech Manufacturing Institute, Georgia Institute of Technology, Atlanta Georgia, USA.
Australian Institute for Machine Learning, University of Adelaide, Adelaide South Australia, Australia.
Siemens Healthineers, Medical Imaging Technologies, Princeton, New Jersey, USA.

Center for Structural Heart Disease, Division of Cardiology, Henry Ford Health System, Detroit, Michigan, USA.

Structural heart disease (SHD) is a new field within cardiovascular medicine. Traditional imaging modalities fall short in supporting the needs of SHD interventions, as they have been constructed around the concept of disease diagnosis. SHD interventions disrupt traditional concepts of imaging in requiring imaging to plan, simulate, and predict intraprocedural outcomes. In transcatheter SHD interventions, the absence of a gold-standard open cavity surgical field deprives physicians of the opportunity for tactile feedback and visual confirmation of cardiac anatomy. Hence, dependency on imaging in periprocedural guidance has led to evolution of a new generation of procedural skillsets, concept of a visual field, and technologies in the periprocedural planning period to accelerate preclinical device development, physician, and patient education. Adaptation of 3-dimensional (3D) printing in clinical care and procedural planning has demonstrated a reduction in early-operator learning curve for transcatheter interventions. Integration of computation modeling to 3D printing has accelerated research and development understanding of fluid mechanics within device testing. Application of 3D printing, computational modeling, and ultimately incorporation of artificial intelligence is changing the landscape of physician training and delivery of patient-centric care. Transcatheter structural heart interventions are requiring in-depth periprocedural understanding of cardiac pathophysiology and device interactions not afforded by traditional imaging metrics.

Center for Health Policy and Health Services Research

Campbell CI, Saxon AJ, Boudreau DM, Wartko PD, Bobb JF, Lee AK, Matthews AG, McCormack J, Liu DS, Addis M, Altschuler A, Samet JH, LaBelle CT, Arnsten J, Caldeiro RM, Borst DT, Stotts AL, **Braciszewski JM**, Szapocznik J, Bart G, Schwartz RP, McNeely J, Liebschutz JM, Tsui JI, Merrill JO, Glass JE, Lapham GT, Murphy SM, Weinstein ZM, Yarborough BJH, and Bradley KA. PRimary Care Opioid Use Disorders treatment (PROUD) trial protocol: a pragmatic, cluster-randomized implementation trial in primary care for opioid use disorder treatment. *Addict Sci Clin Pract* 2021; 16(1):9. PMID: 33517894. Full Text

Division of Research, Kaiser Permanente Northern California, 2000 Broadway, 3rd Floor, Oakland, CA, 94612, USA. cynthia.i.campbell@kp.org.
Center of Excellence in Substance Addiction Treatment and Education, VA Puget Sound Health Care System, 1660 S Columbian Way, Seattle, WA, 98108, USA.
Kaiser Permanente Washington Health Research Institute, 1730 Minor Avenue, Seattle, WA, 98101, USA.
The Emmes Company, 401 N Washington St # 700, Rockville, MD, 20850, USA.
National Institute on Drug Abuse Center for Clinical Trials Network, Three White Flint North, 11601 Landsdown Street, North Bethesda, MD, 20852, USA.
Division of Research, Kaiser Permanente Northern California, 2000 Broadway, 3rd Floor, Oakland, CA, 94612, USA.
Boston Medical Center/Boston University School of Medicine: Clinical Addiction Research & Education (CARE) Unit Crosstown Center, 801 Massachusetts Ave., 2nd Floor, Boston, MA, 02118, USA.
Albert Einstein College of Medicine, Montefiore Medical Center, 3300 Kossuth Avenue, Bronx, NY, 10467, USA.
Kaiser Permanente Washington, 9800 4th Ave. N.E., Seattle, WA, 98115, USA.
Kootenai Clinic Family Medicine, 1919 Lincoln Way, Suite 315, Coeur d Alene, ID, 83814, USA.
Department of Family & Community Medicine, McGovern Medical School, University of Texas Health Science Center at Houston School, 7000 Fannin Street, Houston, TX, 77030, USA.
Department of Psychiatry, Center for Health Policy and Health Services Research, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI, 48202, USA.
Department of Public Health Sciences, University of Miami Miller School of Medicine, 1120 NW 14th Street, 10th Floor, Miami, FL, 33136, USA.
University of Minnesota/Hennepin Healthcare, 701 Park Avenue, Minneapolis, MN, 55415, USA.
Friends Research Institute, 1040 Park Avenue, Suite 103, Baltimore, MD, 21201, USA.
NYU Grossman School of Medicine, 180 Madison Ave., New York, NY, 10016, USA.

Division of General Internal Medicine, Center for Research On Health Care, University of Pittsburgh School of Medicine, 200 Lothrop Street, 933West, Pittsburgh, PA, 15213, USA.
University of Washington/Harborview Medical Center, 325 9th Ave, Seattle, WA, 98104, USA.
Weill Cornell Medical College, 425 East 61st Street, Suite 301, New York, NY, 10065, USA.
Clinical Addiction Research & Education (CARE) Unit, Boston University School of Medicine, Crosstown Center, 801 Massachusetts Ave., 2nd Floor, Boston, MA, 02118, USA.
Kaiser Permanente Northwest, Center for Health Research, 3800 N. Interstate Avenue, Portland, OR, 97227-1098, USA.

BACKGROUND: Most people with opioid use disorder (OUD) never receive treatment. Medication treatment of OUD in primary care is recommended as an approach to increase access to care. The PRimary Care Opioid Use Disorders treatment (PROUD) trial tests whether implementation of a collaborative care model (Massachusetts Model) using a nurse care manager (NCM) to support medication treatment of OUD in primary care increases OUD treatment and improves outcomes. Specifically, it tests whether implementation of collaborative care, compared to usual primary care, increases the number of days of medication for OUD (implementation objective) and reduces acute health care utilization (effectiveness objective). The protocol for the PROUD trial is presented here. METHODS: PROUD is a hybrid type III cluster-randomized implementation trial in six health care systems. The intervention consists of three implementation strategies: salary for a full-time NCM, training and technical assistance for the NCM, and requiring that three primary care providers have DEA waivers to prescribe buprenorphine. Within each health system, two primary care clinics are randomized: one to the intervention and one to Usual Primary Care. The sample includes all patients age 16-90 who visited the randomized primary care clinics from 3 years before to 2 years after randomization (anticipated to be > 170,000). Quantitative data are derived from existing health system administrative data, electronic medical records, and/or health insurance claims ("electronic health records," [EHRs]). Anonymous staff surveys, stakeholder debriefs, and observations from site visits, trainings and technical assistance provide qualitative data to assess barriers and facilitators to implementation. The outcome for the implementation objective (primary outcome) is a clinic-level measure of the number of patient days of medication treatment of OUD over the 2 years post-randomization. The patient-level outcome for the effectiveness objective (secondary outcome) is days of acute care utilization [e.g. urgent care, emergency department (ED) and/or hospitalizations] over 2 years post-randomization among patients with documented OUD prior to randomization. DISCUSSION: The PROUD trial provides information for clinical leaders and policy makers regarding potential benefits for patients and health systems of a collaborative care model for management of OUD in primary care, tested in real-world diverse primary care settings. Trial registration # NCT03407638 (February 28, 2018); CTN-0074 https://clinicaltrials.gov/ct2/show/NCT03407638?term=CTN-0074&draw=2&rank=1.

Center for Health Policy and Health Services Research

Cronin RM, Halvorson AE, Springer C, Feng X, Sulieman L, Loperena-Cortes R, Mayo K, Carroll RJ, Chen Q, **Ahmedani BK**, Karnes J, Korf B, O'Donnell CJ, Qian J, and Ramirez AH. Comparison of family health history in surveys vs electronic health record data mapped to the observational medical outcomes partnership data model in the All of Us Research Program. *J Am Med Inform Assoc* 2021; Epub ahead of print. PMID: 33404595. Full Text

Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
Department of Medicine, The Ohio State University, Columbus, Ohio, USA.
Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Michigan, USA.
Department of Pharmacy Practice and Science, University of Arizona College of Pharmacy, Tuscon, Arizona, USA.
Department of Genetics, University of Alabama at Birmingham, Birmingham, Alabama, USA.
Department of Medicine, Veterans Administration Boston Healthcare System, Boston, Massachusetts, USA.
Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

OBJECTIVE: Family health history is important to clinical care and precision medicine. Prior studies show gaps in data collected from patient surveys and electronic health records (EHRs). The All of Us Research Program collects family history from participants via surveys and EHRs. This Demonstration Project aims to evaluate availability of family health history information within the publicly available data from All of Us and to characterize the data from both sources. MATERIALS AND METHODS: Surveys were completed by participants on an electronic portal. EHR data was mapped to the Observational Medical Outcomes Partnership data model. We used descriptive statistics to perform exploratory analysis of the data, including evaluating a list of medically actionable genetic disorders. We performed a subanalysis on participants who had both survey and EHR data. RESULTS: There were 54 872 participants with family history data. Of those, 26% had EHR data only, 63% had survey only, and 10.5% had data from both sources. There were 35 217 participants with reported family history of a medically actionable genetic disorder (9% from EHR only, 89% from surveys, and 2% from both). In the subanalysis, we found inconsistencies between the surveys and EHRs. More details came from surveys. When both mentioned a similar disease, the source of truth was unclear. CONCLUSIONS: Compiling data from both surveys and EHR can provide a more comprehensive source for family health history, but informatics challenges and opportunities exist. Access to more complete understanding of a person's family health history may provide opportunities for precision medicine.

Center for Health Policy and Health Services Research

Park J, Jindal A, Kuo P, Tanana M, **Lafata JE**, Tai-Seale M, Atkins DC, Imel ZE, and Smyth P. Automated rating of patient and physician emotion in primary care visits. *Patient Educ Couns* 2021; Epub ahead of print. PMID: 33468364. Full Text

Department of Computer Science, University of California, Irvine, USA; Apple Inc., Cupertino, USA. Electronic address: jihyunp@ics.uci.edu.
Department of Computer Science, University of California, Irvine, USA; Hewlett Packard Enterprise, San Jose, USA.
Department of Educational Psychology, University of Utah, Salt Lake City, USA.
Social Research Institute, University of Utah, Salt Lake City, USA.
Division of Pharmaceutical Outcomes and Policy, University of North Carolina at Chapel Hill, USA; Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, USA.
Department of Family Medicine and Public Health, University of California, San Diego, USA.
Department of Psychiatry and Behavioral Science, University of Washington, Seattle, USA.
Department of Educational Psychology, University of Utah, Salt Lake City, USA. Electronic address: zac.imel@utah.edu.
Department of Computer Science, University of California, Irvine, USA. Electronic address: smyth@ics.uci.edu.

OBJECTIVE: Train machine learning models that automatically predict emotional valence of patient and physician in primary care visits. METHODS: Using transcripts from 353 primary care office visits with 350 patients and 84 physicians (Cook, 2002 [1], Tai-Seale et al., 2015 [2]), we developed two machine learning models (a recurrent neural network with a hierarchical structure and a logistic regression classifier) to recognize the emotional valence (positive, negative, neutral) (Posner et al., 2005 [3]) of each utterance. We examined the agreement of human-generated ratings of emotional valence with machine learning model ratings of emotion. RESULTS: The agreement of emotion ratings from the recurrent neural network model with human ratings was comparable to that of human-human inter-rater agreement. The weighted-average of the correlation coefficients for the recurrent neural network model with human raters was 0.60, and the human rater agreement was also 0.60. CONCLUSIONS: The recurrent neural network model predicted the emotional valence of patients and physicians in primary care visits with similar reliability as human raters. PRACTICE IMPLICATIONS: As the first machine learning-based evaluation of emotion recognition in primary care visit conversations, our work provides valuable baselines for future applications that might help monitor patient emotional signals, supporting physicians in empathic communication, or examining the role of emotion in patient-centered care.

Center for Health Policy and Health Services Research

Sala-Hamrick KJ, Isakson B, De Gonzalez SDC, Cooper A, Buchan J, Aceves J, Van Orton E, Holtz J, and Waggoner DM. Trauma-Informed Pediatric Primary Care: Facilitators and Challenges to the Implementation Process. *J Behav Health Serv Res* 2021; Epub ahead of print. PMID: 33415693. Full Text

Henry Ford Health System, Detroit, MI, USA.
University of New Mexico Department of Psychiatry and Behavioral Sciences, MSC09 5030, 1 UNM, Albuquerque, NM, 87131-0001, USA.
University of New Mexico Department of Psychiatry and Behavioral Sciences, MSC09 5030, 1 UNM, Albuquerque, NM, 87131-0001, USA. bisakson@salud.unm.edu.
University of New Mexico Department of Pediatrics, Albuquerque, NM, USA.
University of New Mexico Hospital, Albuquerque, NM, USA.

This article describes the process of integrating trauma-informed behavioral health practices into a pediatric primary care clinic serving low-income and minority families while facing barriers of financial, staffing, and time limitations common to many community healthcare clinics. By using an iterative approach to evaluate each step of the implementation process, the goal was to establish a feasible system in which primary care providers take the lead in addressing traumatic stress. This article describes (1) the process of implementing trauma-informed care into a pediatric primary care clinic, (2) the facilitators and challenges of implementation, and (3) the impact of this implementation process at patient, provider, and community levels. Given the importance of trauma-informed care, especially for families who lack access to quality care, the authors conceptualize this paper as a guide for others attempting to integrate best behavioral health practices into pediatric clinics while working with limited resources.

Dermatology

Collier EK, Price KN, Grogan T, Fernandez JM, Seivright JR, Alhusayen R, Alavi A, **Hamzavi IH**, Lowes MA, Porter MJ, Shi VY, and Hsiao JL. Provider perspectives on the management of hidradenitis suppurativa in pregnancy – A survey study. *International Journal of Women's Dermatology* 2021; Epub ahead of print. PMID: Not assigned. Full Text

J.L. Hsiao, Division of Dermatology, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, United States

Dermatology

Garg A, Malviya N, Strunk A, Wright S, Alavi A, Alhusayen R, Alikhan A, Daveluy SD, Delorme I, Goldfarb N, Gulliver W, **Hamzavi I**, Jaleel T, Kimball AB, Kirby JS, Kirchhof Md MG, Lester J, Lev-Tov H, Lowes MA, Micheletti R, Orenstein LA, Piguet V, Sayed C, Tan J, and Naik HB. Comorbidity screening in Hidradenitis Suppurativa: evidence-based recommendations from the US and Canadian Hidradenitis Suppurativa Foundations. *J Am Acad Dermatol* 2021; Epub ahead of print. PMID: 33493574. Full Text

Department of Dermatology, Donald and Barbara Zucker School of Medicine at Hofstra / Northwell, New Hyde Park, NY, USA. Electronic address: amgarg@northwell.edu.
Department of Dermatology, Donald and Barbara Zucker School of Medicine at Hofstra / Northwell, New Hyde Park, NY, USA.
Division of Dermatology, Faculty of Medicine, Women College Hospital, University of Toronto, Ontario, Canada.
Division of Dermatology, Faculty of Medicine, Women College Hospital, University of Toronto, Ontario, Canada; Department of Medicine and Sunnybrook Research Institute, University of Toronto, Ontario, Canada.
Department of Dermatology, Sutter Medical Foundation, Sacramento, California, USA.
Department of Dermatology, Wayne State University School of Medicine, Detroit, MI, USA.
Dr Isabelle Delorme Inc, Dermatologue, Drummondville, QC, Canada.
Departments of Internal Medicine and Dermatology, Minneapolis VA Health Care System, Minneapolis, MN, USA.
Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada.
Multicultural Dermatology Center, Dept of Dermatology, Henry Ford Hospital, Detroit, MI USA.

Department of Dermatology, Duke University School of Medicine, Durham, NC, USA.
Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA.
Penn State Milton S Hershey Medical Center, Hershey PA, USA.
Division of Dermatology, Faculty of Medicine, University of Ottawa and The Ottawa Hospital, Ottawa, ON, Canada.
Clinical Medical Library, Donald and Barbara Zucker School of Medicine at Hofstra / Northwell, Hempstead, NY, USA.
Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, Miami, FL, USA.
The Rockefeller University, New York, NY, USA.
Deparments of Dermatology and Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.
Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA.
Division of Dermatology, Faculty of Medicine, Women College Hospital, University of Toronto, Ontario, Canada; Women's College Hospital, Toronto, ON, Canada.
Department of Dermatology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill NC, USA.
Department of Internal Medicine, University of Western Ontario, Windsor campus, ON, Canada.
Department of Dermatology, University of California, San Francisco, CA, USA.

BACKGROUND: Hidradenitis suppurativa (HS) is associated with comorbidities that contribute to poor health, impaired life quality, and mortality risk. OBJECTIVE: To provide evidence-based screening recommendations for comorbidities linked to HS. METHODS: Systematic reviews were performed to summarize evidence on prevalence and incidence of 30 comorbidities in HS patients relative to the general population. Screening recommendation for each comorbidity was informed by the consistency and quality of existing studies, disease prevalence and magnitude of association, as well as benefits, harms, and feasibility of screening. Level of evidence and strength of corresponding screening recommendation were graded using SORT criteria. RESULTS: Screening is recommended for the following comorbidities: acne, dissecting cellulitis of the scalp, pilonidal disease, pyoderma gangrenosum, depression, generalized anxiety disorder, suicide, smoking, substance use disorder, polycystic ovarian syndrome, obesity, dyslipidemia, diabetes mellitus, metabolic syndrome, hypertension, cardiovascular disease, inflammatory bowel disease, spondyloarthritis and sexual dysfunction. It is also recommended to screen Down syndrome patients for HS. Decision to screen for specific comorbidities may vary with patient risk factors. The role of the dermatologist in screening varies according to comorbidity. LIMITATIONS: Screening recommendations represent one component of a comprehensive care strategy. CONCLUSIONS: Dermatologists should support screening efforts to identify comorbid conditions in HS.

Dermatology
Kolli SS, Feldman SR, and Huang WW. The dermatology residency application process. *Dermatol Online J* 2021; 26(12). PMID: 33423419. Request Article

Department of Medicine, Henry Ford Hospital, Detroit MI. sreekolli2247@gmail.com.

The dermatology application process is grueling, that is tough to navigate without the proper guidance. This commentary is meant to shed light on the factors that can help applicants stand out in order to be successful in the match. It includes observations from successful applicants from the most recent match process.

Dermatology
Lebwohl MG, **Stein Gold L**, Papp K, Han G, Pariser DM, Lin T, Harris S, and Jacobson A. Long-Term Safety and Efficacy of a Fixed Combination Halobetasol Propionate 0.01%/Tazarotene 0.045% Lotion in Moderate-to-Severe Plaque Psoriasis: Phase 3 Open-Label Study. *J Eur Acad Dermatol Venereol* 2021; Epub ahead of print. PMID: 33428282. Full Text

Icahn School of Medicine at Mount Sinai, New York, NY.
Henry Ford Hospital, Detroit, MI.

Probity Medical Research and K. Papp Clinical Research, Waterloo, Ontario, Canada.
Eastern Virginia Medical School and Virginia Clinical Research, Inc, Norfolk, Virginia.
Ortho Dermatologics, Bridgewater, NJ.
Bausch Health US, LLC is an affiliate of Bausch Health Companies Inc. Ortho Dermatologics is a division of Bausch Health US, LLC.
Bausch Health US, LLC, Bridgewater, NJ.

BACKGROUND: The topical corticosteroid halobetasol propionate (HP) and the retinoid tazarotene (TAZ) are effective in psoriasis treatment. To mitigate adverse cutaneous reactions observed with monotherapy, a fixed-combination HP 0.01%/TAZ 0.045% lotion has been developed for the treatment of plaque psoriasis in adults. OBJECTIVES: To investigate the long-term safety, efficacy, and maintenance of response with HP/TAZ lotion. METHODS: This was a 1-year, multicenter, open-label study in 555 adults with psoriasis (Investigator's Global Assessment [IGA] score of 3 ["moderate"] or 4 ["severe"] and body surface area [BSA] of 3-12% at baseline). HP/TAZ was administered once daily for 8 weeks and then intermittently as needed in 4-week intervals for up to 1 year based on achievement of treatment success (IGA score of 0 ["clear"] or 1 ["almost clear"]). Maximum continuous exposure was 24 weeks. RESULTS: Of 550 participants with post-baseline safety data, 318 (57.8%) achieved treatment success during the study. Of those, 54.4% achieved treatment success within the first 8 weeks; retreatment was not required for >4 weeks in over half (55.3%), and 6.6% did not require any retreatment. Among participants enrolled for the full 52 weeks, 77.5% maintained BSA ≤5% on treatment. There were marked improvements in severity of itching, dryness, and burning/stinging over the study course. The most common treatment-related adverse events were application site reactions of dermatitis, pruritus, pain, and irritation. CONCLUSIONS: Fixed-combination HP/TAZ lotion provided maintained efficacy with a favorable tolerability and safety profile, supporting its use for the long-term treatment and management of moderate-to-severe plaque psoriasis.

Dermatology
McMahon DE, Gallman AE, Hruza GJ, Rosenbach M, Lipoff JB, Desai SR, French LE, **Lim H**, Cyster JG, Fox LP, Fassett MS, and Freeman EE. Long COVID in the skin: a registry analysis of COVID-19 dermatological duration. *Lancet Infect Dis* 2021; Epub ahead of print. PMID: 33460566. Full Text

Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA.
Department of Dermatology, University of California San Francisco, San Francisco, CA, USA; Department of Immunology and Microbiology, University of California San Francisco, San Francisco, CA, USA.
Department of Dermatology, St Louis University, St Louis, MO, USA.
Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA.
Department of Dermatology, University of Texas Southwestern & Innovative Dermatology, Dallas, TX, USA.
Department of Dermatology, University Hospital, Munich University of Ludwig Maximilian, Munich, Germany; Department of Dermatology, Henry Ford Health System, Detroit, MI, USA.
Department of Immunology and Microbiology, University of California San Francisco, San Francisco, CA, USA.
Department of Dermatology, University of California San Francisco, San Francisco, CA, USA.
Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA; Medical Practice Evaluation Center, Mongan Institute, Massachusetts General Hospital, Boston, MA, USA. Electronic address: efreeman@mgh.harvard.edu.

Dermatology
Olds H, **Liu J**, **Luk K**, **Lim HW**, **Ozog D**, and **Rambhatla PV**. Telogen effluvium associated with COVID-19 infection. *Dermatol Ther* 2021; Epub ahead of print. PMID: 33405302. Full Text

Wayne State University School of Medicine, Detroit, Michigan, USA.
Department of Dermatology, Henry Ford Hospital, Detroit, Michigan, USA.

Telogen effluvium (TE) is characterized by diffuse hair shedding 2-3 months after a stressor, and COVID-19 infection is potentially one such stressor. Those who were infected with the virus were under immense psychosocial and physiologic stress. We retrospectively reviewed electronic medical records of 552 patients who were evaluated by a Henry Ford Health System dermatologist between February 2020 and September 2020 and had a diagnosis of COVID-19 infection. Ten patients were identified with TE attributed to COVID-19 infection and described their presentations as a case series. For the ten patients selected, the mean age was 48.5 years old and 90% were female. Six of the patients were Black, one Middle Eastern, and three White. On average, the hair shedding began 50 days after the first symptom of COVID-19 infection. About 80% of these patients were treated with antibiotics, systemic corticosteroids, and/or hydroxychloroquine for their COVID-19 infection and 70% were hospitalized. The presentations of these patients suggest that COVID-19 infection may be a significant trigger of TE. TE caused by hydroxychloroquine, azithromycin or other medications cannot be ruled out, and the global pandemic itself is a source of psychosocial stress. Further studies will be needed to understand the long-term prevalence and prognosis of TE associated with COVID-19 infection.

Dermatology

Zia S, **Shaw B**, **Chapman S**, and **Friedman BJ**. An atypical chondroid syringoma with malignant degeneration: utility of comparative genomic hybridization in confirming the diagnosis. *J Cutan Pathol* 2021; Epub ahead of print. PMID: 33470448. Full Text

Department of Pathology and Laboratory Medicine, Henry Ford Hospital, Detroit, MI.
Department of Dermatology, Henry Ford Hospital, Detroit, MI.

Chondroid syringoma represents the cutaneous counterpart of mixed tumor (pleomorphic adenoma) of salivary glands. Definitive diagnosis is made on histopathology and is based on the presence of characteristic epithelial and stromal components. We report a case of an atypical chondroid syringoma arising on the extremity of an elderly male patient. Histomorphologic features of necrosis and cellular atypia raised suspicion for malignant degeneration, an exceptionally rare circumstance in this context. To further support the diagnosis of malignancy, array comparative genomic hybridization (aCGH) was performed from both low and higher grade areas of the tumor. Both regions demonstrated multiple copy number gains and losses, with additional loss of 17p(TP53), loss of 19p, and loss of heterozygosity (LOH) on16q demonstrated in the more atypical foci. To our knowledge, this is the first case description of malignant degeneration of a chondroid syringoma with correlative microarray analysis. The findings in this case may prove useful in confirming the diagnosis in future ambiguous cases.

Diagnostic Radiology

Cain U, Gaetke-Udager K, **Siegal D**, and Yablon CM. Musculoskeletal Injuries in Pregnancy. *Semin Roentgenol* 2021; 56(1):79-89. PMID: 33422186. Full Text

Musculoskeletal Imaging Fellow, University of Michigan, Ann Arbor, MI.
Department of Radiology, University of Michigan, Ann Arbor, MI. Electronic address: kgaetke@umich.edu.
Department of Radiology, Henry Ford Health System, Detroit, MI.
Department of Radiology, University of Michigan, Ann Arbor, MI.

Diagnostic Radiology

Ivanics T, **Williams P**, **Nasser H**, **Leonard-Murali S**, **Schwartz S**, and **Lin JC**. Contemporary management of chronic indwelling inferior vena cava filters. *J Vasc Surg Venous Lymphat Disord* 2021; 9(1):163-169. PMID: 32721588. Full Text

Department of Surgery, Henry Ford Hospital, Detroit, Mich. Electronic address: tivanic1@hfhs.org.
Vascular and Interventional Radiology, Department of Radiology, Henry Ford Hospital, Detroit, Mich.
Department of Surgery, Henry Ford Hospital, Detroit, Mich.
Division of Vascular Surgery, Department of Surgery, Henry Ford Hospital, Detroit, Mich.

OBJECTIVE: Despite increasing retrieval rates of the inferior vena cava (IVC) filter, less than one-third are removed within the recommended timeline. Prolonged filter dwell times may increase the technical difficulty of retrieval and filter-related complications. We sought to evaluate the contemporary outcomes of patients with chronic indwelling IVC filters at a tertiary care center. METHODS: A retrospective analysis was performed from August 2015 through August 2019 of all patients who were referred for removal of a prolonged IVC filter with a dwell time >1 year. Descriptive analysis was used to evaluate patients' characteristics and procedural outcomes, which were reviewed through electronic medical records. Data were expressed as median with interquartile range (IQR) or number and percentage, as appropriate. RESULTS: A total of 47 patients were identified with a median filter dwell time of 10.0 years (IQR, 6-13 years); 34 patients underwent IVC filter removal, and 13 patients refused retrieval. The median age of patients was 54.9 years (IQR, 42.5-64.0 years); the majority were female (57%) and white (53%). The most common indication for filter placement was high risk despite anticoagulation (49%), followed by venous thromboembolism prophylaxis (21%). The majority of patients were symptomatic (72%). If symptomatic, the most common reason for retrieval was IVC penetration (94%), and the chief complaint was pain (56%). Retrieval success was 97%, with a median length of stay of 0 days. The majority of retrievals were performed through an endovascular approach (97%). There was one postprocedural complication (3%). CONCLUSIONS: Despite prolonged dwell times, IVC filter retrieval can be performed safely and effectively in carefully selected patients at a tertiary referral center.

Diagnostic Radiology

Laucis NC, **Rosen KA**, **Thodge A**, **Leschied JR**, **Klochko CL**, and **Soliman SB**. Sonographic evaluation of the association between calcific tendinopathy and rotator cuff tear: a case-controlled comparison. *Clin Rheumatol* 2021; Epub ahead of print. PMID: 33479863. Full Text

Division of Musculoskeletal Radiology, Department of Radiology, Henry Ford Hospital, Detroit, MI, USA.
Division of Musculoskeletal Radiology, Department of Radiology, Henry Ford Hospital, Detroit, MI, USA. stevens@rad.hfh.edu.

OBJECTIVES: To compare the incidence of rotator cuff (RC) tears on shoulder ultrasounds of patients with RC calcific tendinopathy (CaT) to that of a control group without CaT. METHOD: In this retrospective case-control study, 50 shoulder ultrasounds of patients with CaT were compared independently by 2 musculoskeletal radiologists to 50 patients from a control group without CaT to catalog the number and type of RC tears. RC tears in the CaT group were further characterized based on location, into tears in the specific tendon(s) containing calcium versus all tendon tears. RESULTS: RC tears were diagnosed in 38% (19/50) of the control group (16 full-thickness) as compared to 22% (11/50) with CaT (6 full-thickness). The fewer full-thickness tears in the CaT group (12%, 6 of 50) compared to that in the control group (32%, 16 of 50) was statistically significant (P = 0.016, odds ratio 0.29). Only 7 of the 11 tears in the CaT group were in a calcium-containing tendon (3 full-thickness). The fewer calcium-containing tendon tears compared to tears in the control group was also statistically significant (P = 0.006, odds ratio 0.27). Furthermore, the fewer full-thickness calcium-containing tendon tears (6%, 3/50) compared to full-thickness tears in the control group (32%, 16/50) were yet more statistically significant (P = 0.001, odds ratio 0.14). CONCLUSIONS: In patients with shoulder pain and CaT, we observed a decreased number of RC tears and especially calcium-containing tendon tears, as compared to similar demographic patients with shoulder pain but without CaT. Key Points • Patients with rotator cuff calcific tendinopathy have few rotator cuff tears, especially full-thickness tears, compared to a control group without calcific tendinopathy. • The tendons containing the calcium hydroxyapatite deposition were the least likely to have a rotator cuff tear. • Future studies could evaluate if calcium hydroxyapatite deposition provides a protective mechanism against rotator cuff tears. • Musculoskeletal ultrasound is more sensitive than MRI in the evaluation of rotator cuff calcific tendinopathy.

Diagnostic Radiology

Lee EH, Zheng J, Colak E, Mohammadzadeh M, Houshmand G, **Bevins N**, Kitamura F, Altinmakas E, Reis EP, Kim JK, Klochko C, Han M, Moradian S, Mohammadzadeh A, Sharifian H, Hashemi H, Firouznia K, Ghanaati H, Gity M, Doğan H, Salehinejad H, Alves H, Seekins J, Abdala N, Atasoy Ç, Pouraliakbar H, Maleki M, Wong SS, and Yeom KW. Deep COVID DeteCT: an international experience on COVID-19 lung detection and prognosis using chest CT. *NPJ Digit Med* 2021; 4(1):11. PMID: 33514852. Full Text

Department of Radiology, School of Medicine, Stanford University, Stanford, CA, 94305, USA. edhlee@stanford.edu.
Department of Radiology, School of Medicine, Stanford University, Stanford, CA, 94305, USA.
Unity Health Toronto, University of Toronto, Toronto, ON, M5S, Canada.
Division of Radiology, Amir Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran.
Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.
Henry Ford Health System, Detroit, Michigan, USA.
Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil.
Department of Radiology, Koç University School of Medicine, Istanbul, Turkey.
Hospital Israelita Albert Einstein, São Paulo, Brazil.
Department of Radiology, School of Medicine, Kyungpook National University, Daegu, Korea.
School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Advanced Diagnostic and Interventional Radiology Research Center(ADIR), Medical Imaging Center, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
Department of Electrical Engineering, Stanford University, Stanford, CA, 94305, USA.
Department of Radiology, School of Medicine, Stanford University, Stanford, CA, 94305, USA. kyeom@stanford.edu.

The Coronavirus disease 2019 (COVID-19) presents open questions in how we clinically diagnose and assess disease course. Recently, chest computed tomography (CT) has shown utility for COVID-19 diagnosis. In this study, we developed Deep COVID DeteCT (DCD), a deep learning convolutional neural network (CNN) that uses the entire chest CT volume to automatically predict COVID-19 (COVID+) from non-COVID-19 (COVID-) pneumonia and normal controls. We discuss training strategies and differences in performance across 13 international institutions and 8 countries. The inclusion of non-China sites in training significantly improved classification performance with area under the curve (AUCs) and accuracies above 0.8 on most test sites. Furthermore, using available follow-up scans, we investigate methods to track patient disease course and predict prognosis.

Diagnostic Radiology

Memon AB, Al-Hader R, Patel S, Malik S, Megally M, Steijlen KL, Suri RR, and **Corrigan J**. Late-onset rapidly progressive MRI- negative-myelitis after COVID-19 illness. *Clin Neurol Neurosurg* 2021; 202:106513. PMID: 33517162. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA; Wayne State University, School of Medicine, Detroit, Michigan, USA. Electronic address: AMEMON2@hfhs.org.
Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Radiology, Henry Ford Hospital, Detroit, Michigan, USA; Wayne State University, School of Medicine, Detroit, Michigan, USA.
Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA; Wayne State University, School of Medicine, Detroit, Michigan, USA.

Diagnostic Radiology

Tahir RA, **Affan M**, **Marin H**, **Haider SA**, **Alsrouji OK**, **Ahmad A**, **Chebl AB**, **Katramados A**, **Van Harn M**, and **Kole M**. Quantification of pial collateral pressure in acute large vessel occlusion stroke: basic concept with patient outcomes. *Neuroradiology* 2021; Epub ahead of print. PMID: 33507337. Full Text

Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Radiology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Public Health Sciences, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mkole1@hfhs.org.
Department of Radiology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mkole1@hfhs.org.

PURPOSE: Pial collateral perfusion to the ischemic penumbra plays a critical role in determining patient outcomes in acute stroke. We aimed to assess the validity and reliability of an intra-procedural technique for measuring and quantifying the pial collateral pressure (QPCP) to ischemic brain tissue during acute stroke secondary to LVO. QPCP measurements were correlated with standard computed tomography angiography (CTA) and digital subtraction angiography imaging assessments of pial collateral perfusion and outcomes after mechanical endovascular revascularization (MER). METHODS: This prospective cohort study included 60 consecutive patients with middle cerebral artery (MCA)-M1 and proximal M2 occlusions. QPCP measurements were obtained during MER. The validity of QPCP measurements was evaluated using four widely accepted collateral grading scales. QPCP measurements were also analyzed as a predictor of patient outcomes utilizing National Institute of Health Stroke Scale reduction at 24 h and modified Rankin Scale (mRS) scores at 30 days. RESULTS: QPCP measurements and QPCP ratio (QPCP/systemic mean arterial blood pressure) showed a statistically significant association with single-phase pretreatment CTA Maas and American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology binary grading scales. Patient outcomes demonstrated for every 10-unit increase in QPCP, the odds of mRS 0-2 at 30 days increased by 76% ($p = 0.019$). CONCLUSION: QPCP measurements related best with the pretreatment CTA Maas collateral grading scale but were more strongly associated with patient outcomes than any of the four widely accepted collateral grading scales. Greater QPCP was significantly associated with better overall patient outcomes as defined by mRS at 30 days.

Emergency Medicine

Allen BR, Christenson RH, Cohen SA, **Nowak R**, Wilkerson RG, Mumma B, Madsen T, **McCord J**, Huis In't Veld M, Massoomi M, Stopyra JP, Montero C, Weaver MT, Yang K, and Mahler SA. Diagnostic Performance of High Sensitivity Cardiac Troponin T Strategies and Clinical Variables in a Multisite United States Cohort. *Circulation* 2021; Epub ahead of print. PMID: 33474976. Full Text

Department of Emergency Medicine, College of Medicine, University of Florida, Gainesville, FL.
Department of Pathology, University of Maryland School of Medicine, Baltimore, MD.
Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI.
Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD.
Department of Emergency Medicine, School of Medicine, University of California Davis, Sacramento, CA.
Division of Emergency Medicine, University of Utah School of Medicine, Salt Lake City, UT.
Heart and Vascular Institute and Department of Internal Medicine Henry Ford Hospital, Detroit, MI.
Division of Cardiology, Department of Internal Medicine, College of Medicine, University of Florida, Gainesville, FL.
Department of Emergency Medicine, Wake Forest School of Medicine, Winston-Salem, NC.
Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, FL.
Department of Biostatistics, College of Public Health and Health Professions, University of Florida, Gainesville, FL.

Background: European data support the use of low high-sensitivity troponin (hs-cTn) measurements or a 0/1-hour (0/1-h) algorithm for myocardial infarction (MI) or to exclude major adverse cardiac events (MACE) among Emergency Department (ED) patients with possible acute coronary syndrome (ACS). However, modest US data exist to validate these strategies. This study evaluated the diagnostic performance of an initial hs-cTnT measure below the limit of quantification (LOQ: 6 ng/L), a 0/1-h algorithm, and their combination with HEART scores for excluding MACE in a multisite US cohort. Methods: A prospective cohort study was conducted at 8 US sites, enrolling adult ED patients with symptoms suggestive of ACS and without ST-elevation on electrocardiogram. Baseline and 1-hour blood samples were collected and hs-cTnT (Roche, Basel Switzerland) measured. Treating providers blinded to hs-cTnT results prospectively calculated HEART scores. MACE (cardiac death, MI, and coronary revascularization) at 30-days was adjudicated. The proportion of patients with initial hs-cTnT measures <LOQ and risk based on a 0/1-h algorithm was determined. The negative predictive value (NPV) was calculated for both strategies when used alone or with a HEART score. Results: Among 1,462 participants with initial hs-cTnT measures, 46.4% (678/1,462) were women and 37.1% (542/1,462) were African American with a mean age of 57.6 (SD±12.9) years. MACE at 30-days occurred in 14.4%

(210/1,462). Initial hs-cTnT measures <LOQ occurred in 32.8% (479/1,462), yielding a NPV of 98.3% (95%CI: 96.7-99.3%) for 30-day MACE. A low risk HEART score with an initial hs-cTnT < LOQ occurred in 20.1% (294/1,462) yielding a NPV of 99.0% (95%CI: 97.0-99.8%) for 30-day MACE. A 0/1-h algorithm was complete in 1,430 patients, ruling-out 57.8% (826/1,430) with a NPV of 97.2% (95%CI: 95.9-98.2%) for 30-day MACE. Adding a low HEART score to the 0/1-h algorithm ruled-out 30.8% (441/1430) with a NPV of 98.4% (95%CI: 96.8-99.4%) for 30-day MACE. Conclusions: In a prospective multisite US cohort, an initial hs-cTnT <LOQ combined with a low risk HEART score has 99% NPV for 30-day MACE. The 0/1-h hs-cTnT algorithm did not achieve a NPV > 99% for 30-day MACE when used alone or with a HEART score. Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT02984436.

Emergency Medicine

Harnett NG, van Rooij SJH, **Lewandowski C**, et al. Prognostic neuroimaging biomarkers of trauma-related psychopathology: resting-state fMRI shortly after trauma predicts future PTSD and depression symptoms in the AURORA study. *Neuropsychopharmacology* 2021; Epub ahead of print. PMID: 33479509. Request Article

Neurobiological markers of future susceptibility to posttraumatic stress disorder (PTSD) may facilitate identification of vulnerable individuals in the early aftermath of trauma. Variability in resting-state networks (RSNs), patterns of intrinsic functional connectivity across the brain, has previously been linked to PTSD, and may thus be informative of PTSD susceptibility. The present data are part of an initial analysis from the AURORA study, a longitudinal, multisite study of adverse neuropsychiatric sequalae. Magnetic resonance imaging (MRI) data from 109 recently (i.e., ~2 weeks) traumatized individuals were collected and PTSD and depression symptoms were assessed at 3 months post trauma. We assessed commonly reported RSNs including the default mode network (DMN), central executive network (CEN), and salience network (SN). We also identified a proposed arousal network (AN) composed of a priori brain regions important for PTSD: the amygdala, hippocampus, mamillary bodies, midbrain, and pons. Primary analyses assessed whether variability in functional connectivity at the 2-week imaging timepoint predicted 3-month PTSD symptom severity. Left dorsolateral prefrontal cortex (DLPFC) to AN connectivity at 2 weeks post trauma was negatively related to 3-month PTSD symptoms. Further, right inferior temporal gyrus (ITG) to DMN connectivity was positively related to 3-month PTSD symptoms. Both DLPFC-AN and ITG-DMN connectivity also predicted depression symptoms at 3 months. Our results suggest that, following trauma exposure, acutely assessed variability in RSN connectivity was associated with PTSD symptom severity approximately two and a half months later. However, these patterns may reflect general susceptibility to posttraumatic dysfunction as the imaging patterns were not linked to specific disorder symptoms, at least in the subacute/early chronic phase. The present data suggest that assessment of RSNs in the early aftermath of trauma may be informative of susceptibility to posttraumatic dysfunction, with future work needed to understand neural markers of long-term (e.g., 12 months post trauma) dysfunction. Furthermore, these findings are consistent with neural models suggesting that decreased top-down cortico-limbic regulation and increased network-mediated fear generalization may contribute to ongoing dysfunction in the aftermath of trauma.

Emergency Medicine

Khaldun JS. Public Health Leadership During a Pandemic: Michigan's Experience. *J Public Health Manag Pract* 2021; 27 Suppl 1, COVID-19 and Public Health: Looking Back, Moving Forward:S14-s18. PMID: 33239559. Full Text

Michigan Department of Health and Human Services, Lansing, Michigan; and Department of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan.

Emergency Medicine

Lochner A, **Cesaro R**, and **Chen E**. Rare complication of four extremity compartment syndrome requiring fasciotomy from influenza A viral myositis. *BMJ Case Rep* 2021; 14(1). PMID: 33414112. Full Text

Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan, USA.
Department of Emergency Medicine, Henry Ford Health System, Detroit, Michigan, USA
rcesaro1@hfhs.org.

Influenza A and B commonly cause benign respiratory disease in humans, but can cause more severe illness in high-risk populations. We report an unusual case of a previously healthy adult patient who presented with myositis and severe rhabdomyolysis secondary to influenza A infection that resulted in atraumatic compartment syndrome of all four extremities, each requiring emergent fasciotomy. The patient was subsequently managed with delayed primary closure and skin grafting in the operating room. Prompt recognition of this rare complication by the team resulted in no limb amputations. On his first follow-up appointment, 1 month after discharge, he had regained full functionality in both his hands and his feet were both close to 50% of baseline and improving with physical therapy.

Emergency Medicine

Miller J, Wu Y, Safa R, Marusca G, Bhatti S, **Ahluwalia G**, **Dandashi J**, **Acevedo HG**, **Farook N**, **Scott A**, **Nair V**, **Adhami A**, **Dueweke J**, Hebbar S, and Ekstrom L. Derivation and validation of the ED-SAS score for very early prediction of mortality and morbidity with acute pancreatitis: a retrospective observational study. *BMC Emerg Med* 2021; 21(1):16. PMID: 33509119. Full Text

Henry Ford Hospital, Department of Emergency Medicine, 2799 W Grand Blvd, Detroit, MI, 48202, USA. jmiller6@hfhs.org.
Wayne State University, Detroit, MI, USA. jmiller6@hfhs.org.
Nashville Biosciences, Nashville, TN, USA.
Vanderbilt University Medical Center, Nashville, TN, USA.
Washington University School of Medicine, St. Louis, MO, USA.
Henry Ford Hospital, Department of Emergency Medicine, 2799 W Grand Blvd, Detroit, MI, 48202, USA.
Lake Erie College of Osteopathic Medicine, Erie, PA, USA.
Calcimedica, La Jolla, CA, USA.

BACKGROUND: Existing scoring systems to predict mortality in acute pancreatitis may not be directly applicable to the emergency department (ED). The objective of this study was to derive and validate the ED-SAS, a simple scoring score using variables readily available in the ED to predict mortality in patients with acute pancreatitis. METHODS: This retrospective observational study was performed based on patient data collected from electronic health records across 2 independent health systems; 1 was used for the derivation cohort and the other for the validation cohort. Adult patients who were eligible presented to the ED, required hospital admission, and had a confirmed diagnosis of acute pancreatitis. Patients with chronic or recurrent episodes of pancreatitis were excluded. The primary outcome was 30-day mortality. Analyses tested and derived candidate variables to establish a prediction score, which was subsequently applied to the validation cohort to assess odds ratios for the primary and secondary outcomes. RESULTS: The derivation cohort included 599 patients, and the validation cohort 2011 patients. Thirty-day mortality was 4.2 and 3.9%, respectively. From the derivation cohort, 3 variables were established for use in the predictive scoring score: ≥2 systemic inflammatory response syndrome (SIRS) criteria, age > 60 years, and SpO2 < 96%. Summing the presence or absence of each variable yielded an ED-SAS score ranging from 0 to 3. In the validation cohort, the odds of 30-day mortality increased with each subsequent ED-SAS point: 4.4 (95% CI 1.8-10.8) for 1 point, 12.0 (95% CI 4.9-29.4) for 2 points, and 41.7 (95% CI 15.8-110.1) for 3 points (c-statistic = 0.77). CONCLUSION: An ED-SAS score that incorporates SpO2, age, and SIRS measurements, all of which are available in the ED, provides a rapid method for predicting 30-day mortality in acute pancreatitis.

Emergency Medicine

Nowak RM, **Jacobsen G**, Limkakeng A, Jr., Peacock WF, Christenson RH, **McCord J**, Apple FS, Singer AJ, and deFilippi CR. Outpatient versus observation/inpatient management of emergency department patients rapidly ruled-out for acute myocardial infarction: Findings from the HIGH-US study. *Am Heart J* 2021; 231:6-17. PMID: 33127532. Full Text

Department of Emergency Medicine, Henry Ford Health System, Detroit, MI.
Department of Epidemiology and Statistics, Henry Ford Health System, Detroit, MI.
Division of Emergency, Medicine, Duke University School of Medicine, Durham, NC.
Department of Emergency Medicine, Baylor College of Medicine, Houston, TX.

University of Maryland School of Medicine, Baltimore, MD.
Heart and Vascular Institute, Henry Ford Health System, Detroit, MI.
Department of Laboratory Medicine and Pathology, Hennepin County Medical Center of Hennepin Healthcare and University of Minnesota Minneapolis, Minneapolis, MN.
Department of Emergency Medicine, SUNY Stony Brook, Stony Brook, New York, NY.
Inova Heart and Vascular Institute, Falls Church, VA. Electronic address: Christopher.Defilippi@Inova.org.

BACKGROUND: The actual Emergency Department (ED) dispositions of patients enrolled in observational studies and meeting criteria for rapid acute myocardial infarction (AMI) rule-out are unknown. Additionally, their presenting clinical profiles, cardiac testing/treatments received, and outcomes have not been reported. METHODS: Patients in the HIGH-US study (29 sites) that ruled-out for AMI using a high-sensitivity cardiac troponin I 0/1-hour algorithm were evaluated. Clinical characteristics of patients having ED discharge were compared to patients placed in observation or hospital admitted (OBS/ADM). Reports of any OBS/ADM cardiac stress test (CST), cardiac catheterization (Cath) and coronary revascularization were reviewed. One year AMI/death and major adverse cardiovascular event rates were determined. RESULTS: Of the 1,020 ruled-out AMI patients 584 (57.3%) had ED discharge. The remaining 436 (42.7%) were placed in OBS/ADM. Patients with risk factors for AMI, including personal or family history of coronary artery disease, hypertension, previous stroke or abnormal ECG were more often placed in OBS/ADM. 175 (40.1%) had a CST. Of these 32 (18.3%) were abnormal and 143 (81.7%) normal. Cath was done in 11 (34.3%) of those with abnormal and 13 (9.1%) with normal CST. Of those without an initial CST 85 (32.6%) had Cath. Overall, revascularizations were performed in 26 (6.0%) patients. One-year AMI/death rates were low/similar (P = .553) for the groups studied. CONCLUSIONS: Rapidly ruled-out for AMI ED patients having a higher clinician perceived risk for new or worsening coronary artery disease and placed in OBS/ADM underwent many diagnostic tests, were infrequently revascularized and had excellent outcomes. Alternate efficient strategies for these patients are needed.

Emergency Medicine

Tram J, Pressman A, Chen NW, Berger DA, **Miller J**, Welch RD, Reynolds JC, Pribble J, Hanson I, and Swor R. Percutaneous mechanical circulatory support and survival in patients resuscitated from Out of Hospital cardiac arrest: A study from the CARES surveillance group. *Resuscitation* 2021; 158:122-129. PMID: 33253768. Full Text

Oakland University William Beaumont School of Medicine.
Beaumont Health System- Department of Emergency Medicine.
Division of Informatics and Biostatistics, Beaumont Health.
Department of Emergency Medicine, Henry Ford Health System.
Department of Emergency Medicine, Wayne State University.
Department of Emergency Medicine, Michigan State University.
Department of Emergency Medicine, Michigan Medicine.
Beaumont Health System, Department of Cardiovascular Medicine.
Beaumont Health System- Department of Emergency Medicine. Electronic address: raswor@beaumont.edu.

INTRODUCTION: Maintenance of cardiac function is required for successful outcome after out-of-hospital cardiac arrest (OHCA). Cardiac function can be augmented using a mechanical circulatory support (MCS) device, most commonly an intra-aortic balloon pump (IABP) or Impella®. OBJECTIVE: Our objective is to assess whether the use of a MCS is associated with improved survival in patients resuscitated from OHCA in Michigan. METHODS: We matched cardiac arrest cases during 2014-2017 from the Cardiac Arrest Registry to Enhance Survival (CARES) in Michigan and the Michigan Inpatient Database (MIDB) using probabilistic linkage. Multilevel logistic regression tested the association between MCS and the primary outcome of survival to hospital discharge. RESULTS: A total of 3790 CARES cases were matched with the MIDB and 1131 (29.8%) survived to hospital discharge. A small number were treated with MCS, an IABP (n = 183) or Impella® (n = 50). IABP use was associated with an improved outcome (unadjusted OR = 2.16, 95%CI [1.59, 2.93]), while use of Impella® approached significance (OR = 1.72,

95% CI [0.96, 3.06]). Use of MCS was associated with improved outcome (unadjusted OR = 2.07, 95% CI [1.55, 2.77]). In a multivariable model, MCS use was no longer independently associated with improved outcome (OR(adj) = 0.95, 95% CI [0.69, 1.31]). In the subset of subjects with cardiogenic shock (N = 725), MCS was associated with improved survival in univariate (unadjusted OR = 1.84, 95% CI [1.24, 2.73]) but not multi-variable modeling (OR(adj) = 1.14, 95% CI [0.74, 1.77]). CONCLUSION: Use of MCS was infrequent in patients resuscitated from OHCA and was not independently associated with improvement in post arrest survival after adjusting for covariates.

Endocrinology and Metabolism

Aggarwal A, Pal R, Bhadada SK, Ram S, Garg A, Bhansali A, Singh P, Thakur JS, Singh T, Sachdeva N, and **Rao SD**. Bone mineral density in healthy adult Indian population: the Chandigarh Urban Bone Epidemiological Study (CUBES). *Arch Osteoporos* 2021; 16(1):17. PMID: 33479804. Full Text

Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, 160012, India.
Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, 160012, India. bhadadask@rediffmail.com.
Department of Biochemistry, PGIMER, Chandigarh, India.
Department of Community Medicine, PGIMER, Chandigarh, India.
Department of Radiodiagnosis, PGIMER, Chandigarh, India.
Bone and Mineral Metabolism Laboratory, HFHS, Detroit, MI, USA.

Osteoporosis is a disease with a high burden of morbidity. For its accurate diagnosis, using indigenous data as reference standards is needed. However, normative data on bone density is lacking in India. Therefore, we aimed to determine the reference range for bone density for the healthy population of north India. INTRODUCTION: Osteoporosis is a major public health problem around the globe including India, resulting in significant morbidity, mortality, and health care burden. However, the reference values used for its diagnosis are largely based on data from the western population, which may lead to over- or underdiagnosis of osteoporosis in Indians. Our study aimed to determine the reference range for bone mineral density for the healthy population of India. METHODS: This is a cross-sectional study of 825 subjects (men 380, women 445) (median age: 41 years, IQR 32-55 years), recruited by a house-to-house survey. The population was stratified into decade-wise groups and biochemical measurements including renal and liver function tests, glycated hemoglobin, serum calcium, 25-hydroxyvitamin D, parathyroid hormone, and bone mineral density were performed in all the subjects. The T-scores for men aged > 50 years and post-menopausal women were calculated based on the data generated from this study in young men and women aged 20-40 years. RESULTS: According to the BMD manufacturer's data, which is based on the western population, 70% of the Indian men (> 50 years) and 48% of the post-menopausal Indian women had osteopenia while 18% of the men and 25% of the women had osteoporosis. However, according to the re-calculated T-scores from the current study, only 56% and 7.2% of men and 33% and 5% of women had osteopenia and osteoporosis, respectively. An age-related decline in bone mineral density, as seen in the western population, was also seen in both Indian men and women. CONCLUSION: We have established a reference database for BMD in healthy Indian adult population, which may have clinical implications for the diagnosis and intervention strategies for the management of osteoporosis.

Endocrinology and Metabolism

Dempster DW, Zhou H, **Rao SD**, Recknor C, Miller PD, Leder BZ, Annett M, Ominsky MS, and Mitlak BH. Early Effects of Abaloparatide on Bone Formation and Resorption Indices in Postmenopausal Women With Osteoporosis. *J Bone Miner Res* 2021; Epub ahead of print. PMID: 33434314. Full Text

Regional Bone Center, Helen Hayes Hospital, West Haverstraw, NY, USA.
Bone & Mineral Research Laboratory, Henry Ford Health System, Detroit, MI, USA.
United Osteoporosis Centers, Gainesville, GA, USA.
Colorado Center for Bone Health, Lakewood, CO, USA.
Mass General Hospital, Harvard Medical School, Boston, MA, USA.
Radius Health, Inc., Boston, MA, USA.

Anabolic osteoporosis drugs improve bone mineral density by increasing bone formation. The objective of this study was to evaluate the early effects of abaloparatide on indices of bone formation and to assess the effect of abaloparatide on modeling-based formation (MBF), remodeling-based formation (RBF), and overflow MBF (oMBF) in transiliac bone biopsies. In this open-label, single-arm study, 23 postmenopausal women with osteoporosis were treated with 80 μg abaloparatide daily. Subjects received double fluorochrome labels before treatment and before biopsy collection at 3 months. Change in dynamic histomorphometry indices in four bone envelopes were assessed. Median mineralizing surface per unit of bone surface (MS/BS) increased to 24.7%, 48.7%, 21.4%, and 16.3% of total surface after 3 months of abaloparatide treatment, representing 5.5-, 5.2-, 2.8-, and 12.9-fold changes, on cancellous, endocortical, intracortical, and periosteal surfaces ($p < .001$ versus baseline for all). Mineral apposition rate (MAR) was significantly increased only on intracortical surfaces. Bone formation rate (BFR/BS) was significantly increased on all four bone envelopes. Significant increases versus baseline were observed in MBF on cancellous, endocortical, and periosteal surfaces, for oMBF on cancellous and endocortical surfaces, and for RBF on cancellous, endocortical, and intracortical surfaces. Overall, modeling-based formation (MBF + oMBF) accounted for 37% and 23% of the increase in bone-forming surface on the endocortical and cancellous surfaces, respectively. Changes from baseline in serum biomarkers of bone turnover at either month 1 or month 3 were generally good surrogates for changes in histomorphometric endpoints. In conclusion, treatment with abaloparatide for 3 months stimulated bone formation on cancellous, endocortical, intracortical, and periosteal envelopes in transiliac bone biopsies obtained from postmenopausal women with osteoporosis. These increases reflected stimulation of both remodeling- and modeling-based bone formation, further elucidating the mechanisms by which abaloparatide improves bone mass and lowers fracture risk.

Endocrinology and Metabolism

Farlay D, Rizzo S, Ste-Marie LG, Michou L, Morin SN, Qiu S, Chavassieux P, Chapurlat RD, **Rao SD**, Brown JP, and Boivin G. Duration-Dependent Increase of Human Bone Matrix Mineralization in Long-Term Bisphosphonate Users with Atypical Femur Fracture. *J Bone Miner Res* 2021; Epub ahead of print. PMID: 33434290. Full Text

INSERM, UMR 1033, Université de Lyon, Lyon, France.
Department of Medicine, Université de Montréal, Montréal, Canada.
Division of Rheumatology, Department of Medicine, CHU de Québec-Université Laval Research Centre, Quebec City, Canada.
Department of Medicine McGill University, Montreal, Canada.
Bone & Mineral Research Laboratory, Henry Ford Health System, Detroit, MI, USA.

Bisphosphonates (BPs) are the most widely used drugs for the treatment of osteoporosis but prolonged use of BPs might increase the risk of atypical femur fracture (AFF). There are only a few studies that address the bone material quality in patients on long-term BP treatment with or without AFFs. We analyzed 52 trans-iliac bone biopsies from patients on long-term BP therapy with (n=26) and without (n=26) AFF. At the microscopic level, the degree of mineralization of bone (DMB) was assessed on whole bone by X-ray digitized microradiography while microhardness by Vickers microindentation, and bone matrix characteristics by Fourier Transform Infrared Microspectroscopy (mineral/organic ratio, mineral maturity and crystallinity, and collagen maturity) were measured at random focal areas. The AFF patients were treated longer than non-AFF patients (9.7 ± 3.3 years versus 7.9 ± 2.7 years). As expected, bone remodeling was low in both groups, without difference between them. The AFF group had significantly higher DMB in cortical bone (+2.9%, p=0.001), which remained so after adjusting for treatment duration (p=0.007), and showed a trend in cancellous bone (+1.6%, p=0.05). Consistent with higher DMB, HI was lower in the AFF than in the non-AFF group, illustrating lower heterogeneity of mineralization in the AFF group. A significant positive correlation between the duration of treatment and DMB in cortical bone was found in AFF, and not in the non-AFF group. Microhardness and bone matrix characteristics were similar between groups. We conclude that the AFF group had a duration-dependent increase in DMB leading to a significantly higher DMB than the non-AFF. Because BPs have high affinity to bone mineral and lining

the walls of the osteocyte lacunae, the accumulation of matrix bound BPs in AFF could lead to inhibition of the osteocyte cytoskeleton blunting their response to mechanical strains, a hypothesis to be further investigated.

Gastroenterology
Abdalla T, Lowes MA, **Kaur N**, Micheletti RG, Steinhart AH, and Alavi A. Is There a Role for Therapeutic Drug Monitoring in Patients with Hidradenitis Suppurativa on Tumor Necrosis Factor-α Inhibitors? *Am J Clin Dermatol* 2021; Epub ahead of print. PMID: 33398848. Request Article

Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada.
The Rockefeller University, New York, NY, USA.
Division of Gastroenterology and Hepatology, Henry Ford Health System, Novi, MI, USA.
Department of Dermatology and Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.
Division of Gastroenterology, Department of Medicine, Zane Cohen Center, Mount Sinai Hospital University of Toronto, Toronto, ON, Canada.
Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada. Alavi.Afsaneh@mayo.edu.
Department of Dermatology, Mayo Clinic, Rochester, MN, 55905, USA. Alavi.Afsaneh@mayo.edu.

Tumor necrosis factor-α inhibitors, adalimumab and infliximab, are at the forefront of biologic therapy for the management of moderate-to-severe hidradenitis suppurativa, with adalimumab as currently the only approved medication for this condition. In treating patients, primary or secondary lack of response (also termed suboptimal response) is a major burden for both patients and healthcare systems and is a challenge with biologics in part owing to the development of anti-drug antibodies following treatment. To overcome this, therapeutic drug monitoring may be conducted proactively or reactively to a patient's suboptimal response guided by measurements of trough serum drug concentrations and levels of anti-drug antibodies. While strong evidence to support the utility of therapeutic drug monitoring exists in patients with inflammatory bowel disease, current information is limited in the context of hidradenitis suppurativa. We sought to summarize the available evidence and to present the role of therapeutic drug monitoring and other dose optimization strategies in improving clinical response in patients with hidradenitis suppurativa treated with tumor necrosis factor-α inhibitors.

Gastroenterology
Brown KA. From Heresy to Standard of Care: A Virologic Journey. *Liver Transpl* 2021; Epub ahead of print. PMID: 33460506. Full Text

Gastroenterology and Hepatology, Henry Ford Hospital, 2799 w grand blvd, Detroit, Michigan, USA.

In this month's journal, Bohorquez and colleagues review their experience with transplanting HCV + donor livers into HCV - recipients. In a retrospective analysis, the authors report from June 2018 to December 2019, following verification of DAA access, absence of critical drug-drug interactions and informed consent, allocated HCV NAT + organs were routinely offered to all patients on the waiting list for liver transplant irrespective of recipient HCV status.

Gastroenterology
Kedia SK, Ali B, Jiang Y, Arshad H, Satapathy SK, and **Gonzalez HC**. Post-liver transplant outcomes in patients with major psychiatric diagnosis in the United States. *Ann Hepatol* 2021; Epub ahead of print. PMID: 33482365. Full Text

School of Public Health, University of Memphis, Memphis, TN, USA. Electronic address: skkedia@memphis.edu.
James D Eason Transplant Institute, Methodist University Hospital, University of Tennessee Health Science Center, Memphis, TN, USA. Electronic address: abilal1@uthsc.edu.
School of Public Health, University of Memphis, Memphis, TN, USA. Electronic address: yjiang4@memphis.edu.

School of Public Health, University of Memphis, Memphis, TN, USA. Electronic address: mharshad@memphis.edu.
Division of Hepatology and Sandra Atlas Bass Center for Liver Diseases & Transplantation, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Manhasset, NY, USA. Electronic address: ssatapat@northwell.edu.
Department of Gastroenterology and Hepatology, Henry Ford Health System, Detroit, MI, United States; Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, United States. Electronic address: hgonzal1@hfhs.org.

INTRODUCTION AND OBJECTIVES: Higher rates of psychiatric disorders are reported among cirrhotic patients. This study examines the demographic and clinical outcomes post-liver transplant (LT) among cirrhotic patients with a major psychiatric diagnosis (cases) compared to those without psychiatric diagnosis (controls). MATERIALS AND METHODS: Retrospective case control design was used among 189 cirrhotic patients who had undergone LT at Methodist University Hospital Transplant Institute, Memphis, TN between January 2006 and December 2014. Multivariable regression and Cox proportional hazard regression were conducted to compare allograft loss and all-cause mortality. RESULTS: The study sample consisted of a matched cohort of 95 cases and 94 controls with LT. Females and those with Hepatic Encephalopathy (HE) were more likely to have psychiatric diagnosis. Patients with hepatocellular carcinoma (HCC) were twice as likely to have allograft loss. Psychiatric patients with HCC had two and a half times (HR 2.54; 95% CI: 1.20-5.37; p = 0.015) likelihood of all-cause mortality. Data censored at 1-year post-LT revealed that patients with psychiatric diagnosis have a three to four times higher hazard for allograft loss and all-cause mortality compared to controls after adjusting for covariates, whereas when the data is censored at 5 year, allograft loss and all-cause mortality have two times higher hazard ratio. CONCLUSIONS: The Cox proportional hazard regression analysis of censored data at 1 and 5 year indicate higher allograft loss and all-cause mortality among LT patients with psychiatric diagnosis. Patients with well-controlled psychiatric disorders who undergo LT need close monitoring and medication adherence.

Gastroenterology

Kitajima T, **Henry M**, **Ivanics T**, **Yeddula S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud MS**, **Nagai S**, and **Moonka D**. Incidence and Risk Factors for Fatal Graft-versus-host Disease After Liver Transplantation. *Transplantation* 2021; Epub ahead of print. PMID: 33449608. Full Text

Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI. Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI.

BACKGROUND: Graft-versus-host disease (GVHD) after liver transplantation (LT) is a rare but serious complication. The aim of this study is to identify risk factors, including immunosuppressive regimens, for mortality due to GVHD (fatal GVHD). METHODS: Using data from the OPTN/UNOS registry, 77,416 adult patients who underwent LT between 2003 and 2018 were assessed. Risk factors for fatal GVHD were analyzed by focusing on induction and maintenance immunosuppression regimens. RESULTS: The incidence of fatal GVHD was 0.2% (121/77,416), of whom 105 (87%) died within 180 days and 13 (11%) died between 181 days and 1 year. Median survival after LT was 68.0 (49.5-125.5) days. Recipient age minus donor age greater than 20 years (HR 2.57, P<0.001) and basiliximab induction (HR 1.69, P=0.018) were independent risk factors for fatal GVHD. Maintenance therapy with mycophenolate mofetil (MMF) was associated with a decrease in fatal GVHD (HR 0.51, P=0.001). In an increased risk cohort of patients with recipient-donor age discrepancy greater than 20 years, MMF use was associated with a 50% decline in fatal GVHD (HR 0.50, P<0.001). CONCLUSIONS: Recipient age minus donor age greater than 20 years remains a significant risk factor for fatal GVHD. The risk of fatal GVHD significantly increases in association with basiliximab induction and decreases with MMF maintenance. These associations were pronounced in patients with recipient minus donor age greater than 20 years. These results emphasize the importance of donor age and individualized immunosuppression regimens on the risk of fatal GVHD.

Gastroenterology

Kitajima T, **Moonka D**, **Yeddula S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud MS**, and **Nagai S**. Outcomes in living donor compared to deceased donor primary liver transplant in lower acuity patients with MELD score < 30. *Liver Transpl* 2021; Epub ahead of print. PMID: 33492764. Full Text

Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI, USA.
Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI, USA.

While recent studies have reported favorable outcomes in living donor liver transplantation (LDLT), it remains unclear which populations benefit most from LDLT. The aim of this study is to evaluate post-transplant outcomes in LDLT compared to deceased donor liver transplant (DDLT) according to Model for End-Stage Liver Disease (MELD) score categories. Using data from the OPTN/UNOS registry, outcomes were compared between 1,486 LDLT, 13,568 donation after brain death (DBD) DDLT, and 1,171 donation after circulatory death (DCD) DDLT transplanted between 2009 and 2018. Because LDLT for patients with MELD score >30 was rare (1.8% of all LDLT), all patients with scores > 30 were excluded to equalize LDLT and DDLT cohorts. Risk factors for one-year graft loss were determined in LDLT and DDLT, separately. Compared with LDLT, DBD-DDLT had significantly lower risk of 30-day (aHR 0.60, P<0.001) and one-year graft loss (aHR 0.57, P<0.001). The significantly lower risk of graft loss was more prominent in the mid-MELD score category (score 15-29). DCD-DDLT, compared to LDLT, had significantly lower risk of 30-day graft loss, but comparable risk of one-year graft loss regardless of MELD score category. In LDLT, significant ascites was an independent risk factor for graft loss in patients with mid-MELD scores (aHR 1.68, P=0.02), but not in the lower-MELD score group. Risk of one-year graft loss in LDLT patients with ascites who received left liver was significantly higher than either those who received right liver or those without ascites who received left liver CONCLUSION: In LDLT, combinations of MELD score of 15-29, moderate/severe ascites and use of left liver, are associated with worse outcomes. These findings help calibrate appropriate patient and graft selection in LDLT.

Gastroenterology

Mishra K, **Naffouj S**, **Gorgis S**, **Ibrahim H**, **Gill S**, **Fadel R**, **Chatfield A**, **Tang A**, and **Salgia R**. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. *Hepatol Commun* 2021; 5(1):24-32. PMID: 33437898. Full Text

Department of Internal Medicine Henry Ford Hospital Detroit MI USA.
Division of Cardiology Department of Medicine Henry Ford Hospital Detroit MI USA.
Department of Public Health Sciences Henry Ford Hospital Detroit MI USA.
Division of Gastroenterology and Hepatology Department of Medicine Henry Ford Hospital Detroit MI USA.

Respiratory failure is the most common cause of death in patients with corona virus disease 2019 (COVID-19). There have been many investigations to determine predictors of bad outcomes in patients with this illness. Liver enzyme elevation has been described in hospitalized patients with severe COVID-19; however, little is known about the significance of liver injury regarding outcomes. We conducted a retrospective chart review of 348 patients admitted with COVID-19 in our quaternary care center. Liver injury on admission was defined based on the laboratory cutoff of aspartate aminotransferase >35 IU/L and/or alanine aminotransferase >52 IU/L. Patients were divided into two cohorts based on the presence or absence of liver injury. These cohorts were compared to assess differences in presentation, complications, and outcomes. The primary outcome was respiratory failure requiring intubation, and the secondary outcome was in-hospital mortality. The presence of new onset liver enzyme elevation on presentation was associated with increased severity of illness, need for mechanical ventilation, and mortality. Presence of liver injury increased the chance of acute hypoxic respiratory failure requiring mechanical ventilation by 1.79 times. The degree and timeline of liver enzyme elevation during hospitalization corresponded with elevations of other inflammatory markers. Conclusion: Liver injury appears to correlate with the inflammatory syndrome caused by COVID-19, with the degree of liver injury corresponding with severity of inflammation. We suggest early and continued monitoring of liver enzymes as they can be useful to identify patients who may need early escalation of care.

Gastroenterology

Nagai S, **Safwan M**, **Kitajima T**, **Yeddula S**, **Abouljoud M**, and **Moonka D**. Disease-Specific Waitlist Outcomes in Liver Transplantation. *Transpl Int* 2021; Epub ahead of print. PMID: 33423330. Full Text

Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI, USA.
Division of Gastroenterology, Henry Ford Hospital, Detroit, MI, USA.

This study aimed to evaluate possible discrepancies in waitlist outcomes between liver diseases, including alcohol-related liver disease (ALD), non-alcoholic steatohepatitis (NASH), hepatitis C virus infection (HCV), primary biliary cirrhosis (PBC), and primacy sclerosing cholangitis (PSC). Patients registered for liver transplantation from January 11, 2016 to June 30, 2018 were evaluated using OPTN/UNOS registry. Waitlist outcomes were compared between the five-disease groups. Patients were categorized by initial MELD-Na-score (6-20, 21-29, and ≥30) to identify outcome variations. Prognostic impact of transplantation was assessed according to final MELD-Na scores using Cox-regression analysis modeling transplantation as a time-dependent covariate. 6,053 with ALD, 3,814 with NASH, 1,558 with HCV, 602 with PBC, and 819 with PSC were eligible. Compared to ALD with comparable MELD-Na-scores, NASH with lower (adjusted hazard ratio [aHR]=1.30, P=0.042) and mid-scores (aHR=1.35, P=0.008) showed significantly higher risk of 1-year waitlist mortality, and PBC with higher scores showed significantly higher risk of 90-day (aHR=1.69, P=0.03) and 1-year waitlist mortality (aHR=1.69, P=0.02). Positive prognostic impact of transplantation was not seen until score of 24-27 in ALD, 18-20 in HCV, 15-17 in NASH, and 24-27 in PBC and PSC. There are significant differences in waitlist outcomes among etiologies, which may differ the optimal transplant timing.

Gastroenterology

Sadiq O, **Simmer S**, **Watson A**, **Eng M**, **Frisoli T**, and **Zuchelli T**. Colovaginal fistula closure using a cardiac septal defect occluder. *VideoGIE* 2021; 6(1):41-43. PMID: 33490756. Full Text

Division of Gastroenterology, Henry Ford Hospital, Detroit, Michigan.
Division of Cardiology, Henry Ford Hospital, Detroit, Michigan.

Gastroenterology

Shamaa O, **Jafri SM**, **Shamaa MT**, **Brown K**, and **Venkat D**. Takotsubo Cardiomyopathy Following Liver Transplantation: A Report of 2 Cases. *Transplant Proc* 2021; 53(1):239-243. PMID: 32980136. Full Text

Internal Medicine, Henry Ford Hospital, Detroit, Michigan, United States. Electronic address: Omaar10y@gmail.com.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan, United States.
General Surgery, Henry Ford Hospital, Detroit, Michigan, United States.

PURPOSE: Takotsubo cardiomyopathy, also called apical ballooning syndrome, is characterized by regional left ventricular systolic dysfunction that resembles myocardial infarction in its initial presentation; however, it lacks angiographic evidence of coronary artery disease. We evaluated the incidence of takotsubo cardiomyopathy following liver transplant at a diverse urban transplant program. METHODS: This is a retrospective review of patients transplanted at a single center between 2017 and 2019. Here we report 2 cases of takotsubo cardiomyopathy that developed after liver transplantation. RESULTS: A 65-year-old woman diagnosed with alcoholic cirrhosis underwent a brain-dead donor liver transplant. The postoperative course was complicated by stroke, pulmonary hypertension, and a left internal jugular thrombus. Six months following transplant, the patient developed takotsubo cardiomyopathy with congestive hepatopathy and died of heart failure complications despite maximal medical care. The second case was a 65-year-old woman with alcoholic cirrhosis admitted for a living donor liver transplant. The postoperative period involved recurrent seizures and elevated troponins with markedly reduced ejection fraction, which were appropriately managed. The patient recovered well with supportive care and was discharged to a rehabilitation facility shortly after. CONCLUSION: We present a series of patients with takotsubo cardiomyopathy after liver transplantation. The diagnosis depends on the clinical presentation and findings on electrocardiography, echocardiography, and cardiac enzymes. Our patients met the Mayo Clinic diagnostic criteria and were appropriately managed according to guidelines. Our

report highlights the possibility of pulmonary hypertension contributing to the development of takotsubo cardiomyopathy. Additional studies are needed to establish a definite correlation.

Gastroenterology

Zuchelli T, **Watson A**, and **Piraka C**. Cold snare endoscopic mucosal resection for the removal of large nonpedunculated colon polyps. *VideoGIE* 2021; 6(1):4-6. PMID: 33490743. Full Text

Henry Ford Hospital, Division of Gastroenterology, Detroit, Michigan.

Global Health Initiative

Lucien MAB, Canarie MF, Kilgore PE, Jean-Denis G, Fénélon N, Pierre M, Cerpa M, Joseph GA, **Maki G**, **Zervos MJ**, Dely P, Boncy J, Sati H, Rio AD, and Ramon-Pardo P. Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings. *Int J Infect Dis* 2021; 104:250-254. PMID: 33434666. Full Text

Laboratoire National de Santé Publique, Ministère de la Santé Publique et de la Population, Port-au-Prince, Haiti. Electronic address: lucienmentor@gmail.com.
Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut, USA.
Eugene Applebaum School of Pharmacy, Wayne State University, Detroit, Michigan, USA.
Pan American Health Organization, Haiti.
Laboratoire National de Santé Publique, Ministère de la Santé Publique et de la Population, Port-au-Prince, Haiti.
The Global Health Initiative, Henry Ford Health System, Detroit, Michigan, USA.
Direction d'Épidémiologie, de Laboratoire et de Recherches, Ministère de la Santé Publique et de la Population, Port-au-Prince, Haiti.
Pan American Health Organization, AMR Special Program, Washington DC, USA.

The dissemination of COVID-19 around the globe has been followed by an increased consumption of antibiotics. This is related to the concern for bacterial superinfection in COVID-19 patients. The identification of bacterial pathogens is challenging in low and middle income countries (LMIC), as there are no readily-available and cost-effective clinical or biological markers that can effectively discriminate between bacterial and viral infections. Fortunately, faced with the threat of COVID-19 spread, there has been a growing awareness of the importance of antimicrobial stewardship programs, as well as infection prevention and control measures that could help reduce the microbial load and hence circulation of pathogens, with a reduction in dissemination of antimicrobial resistance. These measures should be improved particularly in developing countries. Studies need to be conducted to evaluate the worldwide evolution of antimicrobial resistance during the COVID-19 pandemic, because pathogens do not respect borders. This issue takes on even greater importance in developing countries, where data on resistance patterns are scarce, conditions for infectious pathogen transmission are optimal, and treatment resources are suboptimal.

Global Health Initiative

Sobeck J, Smith-Darden J, Gartner D, **Kaljee L**, Pieper B, Kilgore P, and **Zervos M**. Antibiotic Knowledge, Beliefs, and Behaviors: Testing Competing Hypotheses Using an Urban Community Sample. *Health Commun* 2021; Epub ahead of print. PMID: 33499691. Request Article

School of Social Work, Wayne State University.
Department of Epidemiology, Gillings School of Public Health, University of North Carolina at Chapel Hill.
Global Health Initiative, Henry Ford Health System.
College of Nursing, Wayne State University.
Department of Pharmacy Practice, Eugene Applebaum Collage of Pharmacy and Health Sciences Wayne State University.
Division of Infectious Diseases, Henry Ford Health System.

Antibiotic use and misuse continue to be a worldwide concern with the increasing rate of antimicrobial resistance, lack of new antibiotics in the pipeline, and rising health care costs. Despite studies that

attempt to distinguish between factors associated with antibiotic use and misuse (e.g., knowledge and beliefs and provider-patient communication), few studies have tested comparative hypotheses related to antibiotic use behavior. This study 1) compares two theoretical models (health belief and patient-centered communication) to learn which best represents the pathways associated with antibiotic use; and 2) describes urban consumers' knowledge, beliefs, and behaviors regarding antibiotic use. Interviewers completed 505 intercept surveys across six clinic- and community-based sites in Southeast Michigan. Structural equation modeling was utilized to compare two competing theoretical models predicting antibiotic behavior. Findings support the assertion that a patient-provider communication model fits the data better than the null model. Descriptive statistical analysis explicated participant knowledge was mixed. While many participants knew correct general facts about antibiotics, 35% of the sample put forth that they believed that antibiotics cure colds and flu and over half (57%) endorsed the belief that antibiotics are good for treating infections caused by viruses. The implications for theory and practice are discussed including the need for clinicians to target communication strategies for the populations that they serve.

Graduate Medical Education

Kolli SS, Feldman SR, and Huang WW. The dermatology residency application process. *Dermatol Online J* 2021; 26(12). PMID: 33423419. Request Article

Department of Medicine, Henry Ford Hospital, Detroit MI. sreekolli2247@gmail.com.

The dermatology application process is grueling, that is tough to navigate without the proper guidance. This commentary is meant to shed light on the factors that can help applicants stand out in order to be successful in the match. It includes observations from successful applicants from the most recent match process.

Hematology-Oncology

Alhamar M, **Alkamachi B**, **Mehrotra H**, **Sanchez J**, **Ali H**, **Schultz D**, and **Chitale DA**. Clinical significance of quantitative categorization of HER2 fluorescent in situ hybridization results in invasive breast cancer patients treated with HER2-targeted agents. *Mod Pathol* 2021; Epub ahead of print. PMID: 33479447. Full Text

Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI, USA.
Department of Hematology and Medical Oncology, Henry Ford Health System, Detroit, MI, USA.
Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI, USA. DCHITAL1@hfhs.org.
Department of Pathology, Wayne State University School of Medicine, Detroit, MI, USA. DCHITAL1@hfhs.org.

HER2 (ERBB2) gene status serves as a strong predictive marker of response to HER2-targeted agents in invasive breast cancers, albeit with heterogeneous response. Our aim was to determine the distribution and prognosis of HER2 groups by fluorescent in situ hybridization (FISH) using the updated 2018 American Society of Clinical Oncology-College of American Pathologist (ASCO-CAP) guidelines. We identified 226 cases of equivocal or positive HER2 FISH invasive breast cancer (interpreted by ASCO-CAP guidelines at the time of reporting) who received HER2-targeted agents from 2006 to 2017. We subcategorized Group 1 further into three subgroups: low amplified (HER2/CEP17 ratio ≥ 2.0-2.99, mean HER2/cell 4.0-5.9), amplified (HER2/CEP17 ratio ≥ 2.0-2.99, mean HER2/cell ≥ 6), and excessive amplification (HER2/CEP17 ratio ≥ 3.0, mean HER2/cell ≥ 4.0). Outcomes studied were recurrence, metastasis, second breast primary, disease-specific survival (DSS), and overall survival (OS). Univariate analysis showed that the five categories of HER2 FISH were significantly associated with OS ($p < 0.01$), specifically higher HER2 amplification was associated with fewer deaths. HER2 FISH status also statistically significantly relates to DFS ($p < 0.01$) and metastasis ($p = 0.01$) but not with recurrence or second breast primary in our study. Tumor type and HER2 ISH Groups are independent predictors for both OS and DFS in our cohort. The proposed Group 1 subcategories were significantly associated with OS ($p < 0.01$) and DFS ($p < 0.01$), excessive HER2 amplification was associated with longer median survival. The Cox regression models showed better survival outcomes for the excessive amplification

subgroup than the low amplified subgroup, with OS (hazard ratio = 0.63, 95% CI 0.42-0.93) and DFS (HR = 0.55, 95% CI 0.37-0.83). We demonstrated that in HER2 FISH Group 1 patients, high HER2 amplification was significantly associated with longer OS and DFS; these patients seem to benefit more from HER2-targeted regimens. We recommend reporting these Group 1 subcategories when assessing HER2 FISH.

Hematology-Oncology

Hurtado FK, de Braud F, De Castro Carpeño J, de Miguel Luken MJ, **Wang D**, Scott J, Lau YY, McCulloch T, and Mau-Sorensen M. Effect of ceritinib on the pharmacokinetics of coadministered CYP3A and 2C9 substrates: a phase I, multicenter, drug-drug interaction study in patients with ALK + advanced tumors. *Cancer Chemother Pharmacol* 2021; Epub ahead of print. PMID: 33394101. Full Text

Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.
felipe.kellermann_hurtado@novartis.com.
Fondazione IRCCS-Istituto Nazionale Dei Tumori, Milano, Italy.
Medical Oncology Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain.
CIOCC-Grupo Hospitalario de Madrid, Hosp. de Sanchinarro, Madrid, Spain.
Henry Ford Cancer Institute, Detroit, MI, USA.
Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.
Department of Oncology, Rigshospitalet, Copenhagen, Denmark.

PURPOSE: Ceritinib is an ALK receptor tyrosine kinase inhibitor approved as first- and second-line treatment in adult patients with ALK + metastatic non-small cell lung cancer (NSCLC). The study investigated the drug-drug interaction (DDI) potential of ceritinib when coadministered with midazolam and warfarin as probe substrates for CYP3A and CYP2C9 activity, respectively. METHODS: This was a phase I, multicenter, open-label, single sequence, crossover DDI study in 33 adult patients with ALK + NSCLC or other advanced tumors. A single dose of a cocktail consisting of midazolam and warfarin was administered with and without concomitant administration of ceritinib. The primary objective was to evaluate the pharmacokinetics of midazolam and warfarin. Secondary objectives included pharmacokinetics, safety, tolerability, overall response rate (ORR), and duration of response (DOR) of ceritinib 750 mg once daily. RESULTS: Ceritinib inhibited CYP3A-mediated metabolism of midazolam, resulting in a markedly increased AUC (geometric mean ratio [90% confidence interval]) by 5.4-fold (4.6, 6.3). Ceritinib also led to an increase in the AUC of S-warfarin by 54% (36%, 75%). The pharmacokinetics and safety profile of ceritinib in this study are consistent with previous reports and no new safety signals were reported. Among the 19 patients with NSCLC, efficacy (ORR: 42.1% and DCR: 63.2%) was similar to that reported previously in studies of pretreated patients with ALK + NSCLC. CONCLUSION: Ceritinib is a strong CYP3A inhibitor and a weak CYP2C9 inhibitor. These findings should be reflected as actionable clinical recommendations in the prescribing information for ceritinib with regards to concomitant medications whose pharmacokinetics may be altered by ceritinib.

Hematology-Oncology

Mosalem O, Alsara A, **Abu Rous F**, and Hrinczenko B. Adenoid cystic carcinoma of the labium oris with rare metastasis to the pleural cavity. *BMJ Case Rep* 2021; 14(1). PMID: 33414116. Full Text

Department of Medicine, Michigan State University, East Lansing, Michigan, USA Mosalemo@msu.edu.
Department of Medicine, Sparrow Health System, Lansing, Michigan, USA.
Hematology and Oncology, MidMichigan Health, Michigan State Unviersity, Midland, Michigan, USA.
Hematology and Oncology, Henry Ford Hospital, Detroit, Michigan, USA.
Hematology and Oncology, Michigan State University, Lansing, Michigan, USA.

A 57-year-old Southeast Asian woman with a remote history of adenoid cystic carcinoma (ACC) of the right labium superius oris (upper lip) presented to the hospital with vague epigastric pain. On workup, she was found to have multiple pleural nodules. Histopathology confirmed the diagnosis of metastatic ACC. After 8 months of active surveillance, evidence of disease progression was found and the patient was started on pembrolizumab. Follow-up after starting pembrolizumab showed stable disease with no significant side effects.

Hematology-Oncology

Vaishampayan UN, Heilbrun LK, Monk P, 3rd, Tejwani S, Sonpavde G, **Hwang C**, Smith D, Jasti P, Dobson K, Dickow B, Heath EI, Semaan L, Cher ML, Fontana JA, and Chinni S. Clinical Efficacy of Enzalutamide vs Bicalutamide Combined With Androgen Deprivation Therapy in Men With Metastatic Hormone-Sensitive Prostate Cancer: A Randomized Clinical Trial. *JAMA Netw Open* 2021; 4(1):e2034633. PMID: 33496795. Full Text

Department of Oncology, Karmanos Cancer Center, Wayne State University, Detroit, Michigan.
Department of Internal Medicine, University of Michigan, Ann Arbor.
Department of Internal Medicine, The Ohio State University, Columbus.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Department of Internal Medicine, Dana Farber Cancer Institute, Boston, Massachusetts.
John D. Dingell Veterans Affairs Medical Center, Detroit, Michigan.
Department of Urology, Wayne State University, Detroit, Michigan.

IMPORTANCE: Black patients have been underrepresented in prospective clinical trials of advanced prostate cancer. This study evaluated the efficacy of enzalutamide compared with bicalutamide, with planned subset analysis of Black patients with metastatic hormone-sensitive prostate cancer (mHSPC), which is a disease state responsive to androgen deprivation therapy (ADT). OBJECTIVE: To compare the efficacy of enzalutamide vs bicalutamide in combination with ADT in men with mHSPC, with a subset analysis of Black patients. DESIGN, SETTING, AND PARTICIPANTS: In this randomized clinical trial, a phase 2 screening design enabled a nondefinitive comparison of the primary outcome by treatment. Patients were stratified by race (Black or other) and bone pain (present or absent). Accrual of at least 30% Black patients was required. This multicenter trial was conducted at 4 centers in the US. Men with mHSPC with no history of seizures and adequate marrow, renal, and liver function were eligible. Data analysis was performed from February 2019 to March 2020. INTERVENTIONS: Participants were randomized 1:1 to receive oral enzalutamide (160 mg daily) or bicalutamide (50 mg daily) in addition to ADT. MAIN OUTCOMES AND MEASURES: The primary end point was the 7-month prostate-specific antigen (PSA) response (SMPR) rate, a previously accepted surrogate for overall survival (OS) outcome. Secondary end points included adverse reactions, time to PSA progression, and OS. RESULTS: A total of 71 men (median [range] age, 65 [51-86] years) were enrolled; 29 (41%) were Black, 41 (58%) were White, and 1 (1%) was Asian. Thirty-six patients were randomized to receive enzalutamide, and 35 were randomized to receive bicalutamide. Twenty-six patients (37%) had bone pain and 37 patients (52%) had extensive disease. SMPR was achieved in 30 of 32 patients (94%; 95% CI, 80%-98%) taking enzalutamide and 17 of 26 patients (65%; 95% CI, 46%-81%) taking bicalutamide (P = .008) (difference, 29%; 95% CI, 5%-50%). Among Black patients, the SMPR was 93% (95% CI, 69%-99%) among those taking enzalutamide and 42% (95% CI, 19%-68%) among those taking bicalutamide (P = .009); among non-Black patients, the SMPR was 94% (95% CI, 74%-99%) among those taking enzalutamide and 86% (95% CI, 60%-96%) among those taking bicalutamide. The 12-month PSA response rates were 84% with enzalutamide and 34% with bicalutamide. CONCLUSIONS AND RELEVANCE: The findings of this randomized clinical trial comparing enzalutamide with bicalutamide suggest that enzalutamide is associated with improved outcomes compared with bicalutamide, in terms of the rate and duration of PSA response, in Black patients with mHSPC. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT02058706.

Hospital Medicine

Gunasekaran K, Murthi S, Elango K, Rahi MS, **Thilagar B**, Ramalingam S, Voruganti D, Paramasivam VK, Kolandaivel KP, Arora A, and Chandran A. The Impact of Diabetes Mellitus in Patients with Chronic Obstructive Pulmonary Disease (COPD) Hospitalization. *J Clin Med* 2021; 10(2). PMID: 33440707. Full Text

Division of Pulmonary Diseases and Critical Care, Yale-New Haven Health Bridgeport Hospital, 267 Grant Street, Bridgeport, CT 06610, USA.
Division of Endocrinology and Metabolism, Lenox Hill Hospital, 110 e 59th Street, New York, NY 10022, USA.

Department of Cardiology, University of Nevada Las Vegas, 1701 W Charleston Blvd, Las Vegas, NV 89102, USA.
Division of Hospital Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202, USA.
Division of Hospital Medicine, Lovelace Medical Center, 601 Dr. Martin Luther King Jr. Ave NE, Albuquerque, NM 87102, USA.
Division of Cardiology, University of Arkansan Medical Sciences, 4301 W Markham Street, Little Rock, AR 72205, USA.
Division of Nephrology, Bay State Medical Center, S 759 Chestnut Street, Springfield, MA 01199, USA.
Division of Oncology, St. Joseph Medical Center, 523 N 3rd Street, Brainerd, MN 56401, USA.
Division of Pulmonary Diseases and Critical Care, Saint Mary's Hospital, 56 Franklin Street, Waterbury, CT 06610, USA.
Division of Pulmonary Diseases and Critical Care, Hurley Medical Center, G-3252 Beecher Road, Flint, MI 48532, USA.

(1) Background: Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality worldwide. Diabetes mellitus (DM) has been shown to have adverse inflammatory effects on lung anatomy and physiology. We investigated the impact of DM on COPD patient outcomes during inpatient hospitalization. (2) Methods: We conducted a retrospective analysis using the Nationwide Inpatient Sample (NIS) over the years 2002-2014. Three groups, COPD without diabetes, COPD with diabetes but no complication, and COPD with DM and complication, were analyzed. (3) Results: A total of 7,498,577 were COPD hospitalization; of those, 1,799,637 had DM without complications, and 483,467 had DM with complications. After adjusting for clinical, demographic, and comorbidities, the odds of increased LOS in the COPD/DM with complication were 1.37 (confidence interval (CI): 1.326-1.368), and those of DM without complication were 1.061 (1.052-1.070) when compared with COPD alone. The odds of pneumonia, respiratory failure, stroke, and acute kidney injury were also higher in COPD hospitalizations with DM. Both DM with complication (odds ratio (OR): 0.751 (CI 0.727-0.777)) and DM without complication (OR: 0.635 (CI: 0.596-0.675)) have lesser odds of mortality during hospitalization than with COPD alone. (4) Conclusions: There is a considerable inpatient burden among COPD patients with DM in the United States.

Hypertension and Vascular Research
Roy B, and **Palaniyandi SS**. A role for aldehyde dehydrogenase (ALDH) 2 in angiotensin II-mediated decrease in angiogenesis of coronary endothelial cells. *Microvasc Res* 2021; 135:104133. PMID: 33428883. Request Article

Division of Hypertension and Vascular Research, Department of Internal Medicine, Henry Ford Health System, Detroit, MI 48202, United States of America; Department of Physiology, Wayne State University, Detroit, MI 48202, United States of America.
Division of Hypertension and Vascular Research, Department of Internal Medicine, Henry Ford Health System, Detroit, MI 48202, United States of America; Department of Physiology, Wayne State University, Detroit, MI 48202, United States of America. Electronic address: spalani2@hfhs.org.

Diabetes-induced coronary endothelial cell (CEC) dysfunction contributes to diabetic heart diseases. Angiotensin II (Ang II), a vasoactive hormone, is upregulated in diabetes, and is reported to increase oxidative stress in CECs. 4-hydroxy-2-nonenal (4HNE), a key lipid peroxidation product, causes cellular dysfunction by forming adducts with proteins. By detoxifying 4HNE, aldehyde dehydrogenase (ALDH) 2 reduces 4HNE mediated proteotoxicity and confers cytoprotection. Thus, we hypothesize that ALDH2 improves Ang II-mediated defective CEC angiogenesis by decreasing 4HNE-mediated cytotoxicity. To test our hypothesis, we treated the cultured mouse CECs (MCECs) with Ang II (0.1, 1 and 10 μM) for 2, 4 and 6 h. Next, we treated MCECs with Alda-1 (10 μM), an ALDH2 activator or disulfiram (2.5 μM)/ALDH2 siRNA (1.25 nM), the ALDH2 inhibitors, or blockers of angiotensin II type-1 and 2 receptors i.e. Losartan and PD0123319 respectively before challenging MCECs with 10 μM Ang II. We found that 10 μM Ang II decreased tube formation in MCECs with in vitro angiogenesis assay ($P < .0005$ vs control). 10 μM Ang II downregulated the levels of vascular endothelial growth factor receptor 1 (VEGFR1) ($p < .005$ for mRNA and $P < .05$ for protein) and VEGFR2 ($p < .05$ for mRNA and $P < .005$ for protein) as well as upregulated the levels of angiotensin II type-2 receptor (AT2R) ($p < .05$ for mRNA and $P < .005$ for protein) and 4HNE-

adducts (P < .05 for protein) in cultured MCECs, compared to controls. ALDH2 inhibition with disulfiram/ALDH2 siRNA exacerbated 10 μM Ang II-induced decrease in coronary angiogenesis (P < .005) by decreasing the levels of VEGFR1 (P < .005 for mRNA and P < .05 for protein) and VEGFR2 (P < .05 for both mRNA and protein) and increasing the levels of AT2R (P < .05 for both mRNA and protein) and 4HNE-adducts (P < .05 for protein) relative to Ang II alone. AT2R inhibition per se improved angiogenesis in MCECs. Additionally, enhancing ALDH2 activity with Alda 1 rescued Ang II-induced decrease in angiogenesis by increasing the levels of VEGFR1, VEGFR2 and decreasing the levels of AT2R. In summary, ALDH2 can be an important target in reducing 4HNE-induced proteotoxicity and improving angiogenesis in MCECs. Finally, we conclude ALDH2 activation can be a therapeutic strategy to improve coronary angiogenesis to ameliorate cardiometabolic diseases.

Hypertension and Vascular Research

VasanthiDharmalingam P, Karuppagounder V, Watanabe K, Karmouty-Quintana H, **Palaniyandi SS**, Guha A, and Thandavarayan RA. SARS-CoV-2-mediated hyperferritinemia and cardiac arrest: preliminary insights. *Drug Discov Today* 2021; Epub ahead of print. PMID: 33493677. Full Text

Clone Gene Biosystems, Chennai, 600 018 Tamil Nadu, India.
Center for Orthopedic Research and Translational Sciences, Department of Orthopedics and Rehabilitation, Penn State College of Medicine, Hershey, 17033 PA, USA.
Department of Laboratory Medicine and Clinical Epidemiology for Prevention of Noncommunicable Diseases, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori Chuo-ku, Niigata 951-8510, Japan.
Department of Internal Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas, USA.
Division of Hypertension and Vascular Research, Henry Ford Health System, Detroit, MI 48202, USA.
Houston Methodist DeBakey Heart & Vascular Center, 6550 Fannin Street, Houston, TX 77030, USA.
Houston Methodist DeBakey Heart & Vascular Center, 6550 Fannin Street, Houston, TX 77030, USA.
Electronic address: ramirthalingamthandavarayan@houstonmethodist.org.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic that began in China, was first noted in December 2019. SARS-CoV-2 infects through the angiotensin-converting enzyme-2 (ACE-2) receptor and co-receptors. In the most severely affected patients, it can cause pneumonia and multiple organ failure leading to death. Reports describe high death rates resulting from cardiac dysfunction, a co-morbid condition in SARS-CoV-2 patients, while the primary cause and mechanisms remain unknown. Here, we attempt to review clinical reports of SARS-CoV-2 patients in order to provide insight into a possible mechanism that allows hyperferritinemia (the presence of excess iron-binding protein) to cause cardiac dysfunction in SARS-CoV-2 patients. Such insights are an important avenue towards understanding the mechanism of cardiac dysfunction in SARS-CoV-2 patients and developing remedies for the same.

Infectious Diseases

Craig JR, Tataryn RW, Cha BY, **Bhargava P**, Pokorny A, Gray ST, Mattos JL, and Poetker DM. Diagnosing odontogenic sinusitis of endodontic origin: A multidisciplinary literature review. *Am J Otolaryngol* 2021; 42(3):102925. PMID: 33486208. Full Text

Henry Ford Health System, Department of Otolaryngology- Head and Neck Surgery, Detroit, MI, United States of America. Electronic address: jcraig1@hfhs.org.
Tataryn Endodontics, Spokane, WA, United States of America; Loma Linda University, Department of Endodontics, School of Dentistry, Loma Linda, CA, United States of America.
University of Connecticut, Division of Endodontology, School of Dental Medicine, Farmington, CT, United States of America.
Henry Ford Health System, Department of Internal Medicine, Division of Infectious Disease, Detroit, MI, United States of America.
Spokane ENT Clinic, Spokane, WA, United States of America; University of Washington, Department of Otolaryngology- Head and Neck Surgery, Seattle, WA, United States of America.

Harvard Medical School, Department of Otolaryngology- Head and Neck Surgery, Boston, MA, United States of America.
University of Virginia, Department of Otolaryngology- Head and Neck Surgery, Charlottesville, VA, United States of America.
Medical College of Wisconsin, Department of Otolaryngology- Head and Neck Surgery, Milwaukee, WI, United States of America; Zablocki VAMC, Division of Surgery, Milwaukee, WI, United States of America.

PURPOSE: Endodontic disease is one of the most common causes of bacterial odontogenic sinusitis (ODS). Diagnosing ODS of endodontic origin involves otolaryngologists confirming sinusitis, and dental specialists confirming endodontic sources. The purpose of this study was to conduct a multidisciplinary literature review to highlight clinical and microbiological features of ODS, and the most optimal diagnostic modalities to confirm endodontic disease. METHODS: An extensive review of both medical and dental literature was performed by rhinologists, endodontists, and an infectious disease specialist. Frequencies of various clinical and microbiological features from ODS studies were collected, and averages were calculated. Different endodontic testing and imaging modalities were also evaluated on their abilities to confirm endodontic disease. RESULTS: ODS patients most often present with unilateral sinonasal symptoms for over 3 months, purulence on nasal endoscopy, and overt dental pathology on computed tomography (CT). Subjective foul smell, and maxillary sinus cultures demonstrating anaerobes and α-streptococci (viridans group) may be more specific to ODS. For endodontic evaluations, cold pulp testing and cone-beam CT imaging are most optimal for confirming pulpal and periapical disease. CONCLUSION: Diagnosing ODS requires collaboration between otolaryngologists and dental specialists. Clinicians should suspect ODS when patients present with unilateral sinonasal symptoms, especially foul smell. Patients will generally have purulent drainage on nasal endoscopy, and both sinus opacification and overt dental pathology on CT. However, some patients will have subtle or absent dental pathology on CT. For suspected endodontic disease, endodontists should be consulted for at least cold pulp testing, and ideally cone-beam CT.

Infectious Diseases

Quan D, Luna Wong L, **Shallal A**, Madan R, Hamdan A, Ahdi H, Daneshvar A, Mahajan M, Nasereldin M, **Van Harn M**, Opara IN, and **Zervos M**. Impact of Race and Socioeconomic Status on Outcomes in Patients Hospitalized with COVID-19. *J Gen Intern Med* 2021; Epub ahead of print. PMID: 33506402. Full Text

Wayne State University School of Medicine, Detroit, MI, USA.
Department of Infectious Disease, Henry Ford Hospital, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA.
Department of Internal Medicine, Internal Medicine-Pediatrics Section, Wayne State University School of Medicine, Detroit, MI, USA.
Global Affairs Professor of Medicine, Assistant Dean Wayne State University School of Medicine, MI, Detroit, USA. mzervos1@hfhs.org.
Infectious Diseases, Division Head Henry Ford Health System, MI, Detroit, USA. mzervos1@hfhs.org.

BACKGROUND: The impact of race and socioeconomic status on clinical outcomes has not been quantified in patients hospitalized with coronavirus disease 2019 (COVID-19). OBJECTIVE: To evaluate the association between patient sociodemographics and neighborhood disadvantage with frequencies of death, invasive mechanical ventilation (IMV), and intensive care unit (ICU) admission in patients hospitalized with COVID-19. DESIGN: Retrospective cohort study. SETTING: Four hospitals in an integrated health system serving southeast Michigan. PARTICIPANTS: Adult patients admitted to the hospital with a COVID-19 diagnosis confirmed by polymerase chain reaction. MAIN MEASURES: Patient sociodemographics, comorbidities, and clinical outcomes were collected. Neighborhood socioeconomic variables were obtained at the census tract level from the 2018 American Community Survey. Relationships between neighborhood median income and clinical outcomes were evaluated using multivariate logistic regression models, controlling for patient age, sex, race, Charlson Comorbidity Index, obesity, smoking status, and living environment. KEY RESULTS: Black patients lived in significantly poorer neighborhoods than White patients (median income: $34,758 (24,531-56,095) vs. $63,317 (49,850-85,776), $p < 0.001$) and were more likely to have Medicaid insurance (19.4% vs. 11.2%, $p <$

0.001). Patients from neighborhoods with lower median income were significantly more likely to require IMV (lowest quartile: 25.4%, highest quartile: 16.0%, p < 0.001) and ICU admission (35.2%, 19.9%, p < 0.001). After adjusting for age, sex, race, and comorbidities, higher neighborhood income ($10,000 increase) remained a significant negative predictor for IMV (OR: 0.95 (95% CI 0.91, 0.99), p = 0.02) and ICU admission (OR: 0.92 (95% CI 0.89, 0.96), p < 0.001). CONCLUSIONS: Neighborhood disadvantage, which is closely associated with race, is a predictor of poor clinical outcomes in COVID-19. Measures of neighborhood disadvantage should be used to inform policies that aim to reduce COVID-19 disparities in the Black community.

Infectious Diseases

Sobeck J, Smith-Darden J, Gartner D, **Kaljee L**, Pieper B, Kilgore P, and **Zervos M**. Antibiotic Knowledge, Beliefs, and Behaviors: Testing Competing Hypotheses Using an Urban Community Sample. *Health Commun* 2021; Epub ahead of print. PMID: 33499691. Request Article

School of Social Work, Wayne State University.
Department of Epidemiology, Gillings School of Public Health, University of North Carolina at Chapel Hill.
Global Health Initiative, Henry Ford Health System.
College of Nursing, Wayne State University.
Department of Pharmacy Practice, Eugene Applebaum Collage of Pharmacy and Health Sciences Wayne State University.
Division of Infectious Diseases, Henry Ford Health System.

Antibiotic use and misuse continue to be a worldwide concern with the increasing rate of antimicrobial resistance, lack of new antibiotics in the pipeline, and rising health care costs. Despite studies that attempt to distinguish between factors associated with antibiotic use and misuse (e.g., knowledge and beliefs and provider-patient communication), few studies have tested comparative hypotheses related to antibiotic use behavior. This study 1) compares two theoretical models (health belief and patient-centered communication) to learn which best represents the pathways associated with antibiotic use; and 2) describes urban consumers' knowledge, beliefs, and behaviors regarding antibiotic use. Interviewers completed 505 intercept surveys across six clinic- and community-based sites in Southeast Michigan. Structural equation modeling was utilized to compare two competing theoretical models predicting antibiotic behavior. Findings support the assertion that a patient-provider communication model fits the data better than the null model. Descriptive statistical analysis explicated participant knowledge was mixed. While many participants knew correct general facts about antibiotics, 35% of the sample put forth that they believed that antibiotics cure colds and flu and over half (57%) endorsed the belief that antibiotics are good for treating infections caused by viruses. The implications for theory and practice are discussed including the need for clinicians to target communication strategies for the populations that they serve.

Internal Medicine

Ichkhanian Y, Yang J, and Khashab MA. Response. *Gastrointest Endosc* 2021; 93(1):279-280. PMID: 33353631. Full Text

Division of Gastroenterology and Hepatology, Johns Hopkins Medical Institution, Baltimore, Maryland; Department of Medicine, Henry Ford Hospital, Detroit, Michigan.
Division of Gastroenterology and Hepatology, Vanderbilt University Medical Center, Nashville, Tennessee.
Division of Gastroenterology and Hepatology, Johns Hopkins Medical Institution, Baltimore, Maryland, USA.

Internal Medicine

Mishra K, **Naffouj S**, **Gorgis S**, **Ibrahim H**, **Gill S**, **Fadel R**, **Chatfield A**, **Tang A**, and **Salgia R**. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. *Hepatol Commun* 2021; 5(1):24-32. PMID: 33437898. Full Text

Department of Internal Medicine Henry Ford Hospital Detroit MI USA.

Division of Cardiology Department of Medicine Henry Ford Hospital Detroit MI USA.
Department of Public Health Sciences Henry Ford Hospital Detroit MI USA.
Division of Gastroenterology and Hepatology Department of Medicine Henry Ford Hospital Detroit MI USA.

Respiratory failure is the most common cause of death in patients with corona virus disease 2019 (COVID-19). There have been many investigations to determine predictors of bad outcomes in patients with this illness. Liver enzyme elevation has been described in hospitalized patients with severe COVID-19; however, little is known about the significance of liver injury regarding outcomes. We conducted a retrospective chart review of 348 patients admitted with COVID-19 in our quaternary care center. Liver injury on admission was defined based on the laboratory cutoff of aspartate aminotransferase >35 IU/L and/or alanine aminotransferase >52 IU/L. Patients were divided into two cohorts based on the presence or absence of liver injury. These cohorts were compared to assess differences in presentation, complications, and outcomes. The primary outcome was respiratory failure requiring intubation, and the secondary outcome was in-hospital mortality. The presence of new onset liver enzyme elevation on presentation was associated with increased severity of illness, need for mechanical ventilation, and mortality. Presence of liver injury increased the chance of acute hypoxic respiratory failure requiring mechanical ventilation by 1.79 times. The degree and timeline of liver enzyme elevation during hospitalization corresponded with elevations of other inflammatory markers. Conclusion: Liver injury appears to correlate with the inflammatory syndrome caused by COVID-19, with the degree of liver injury corresponding with severity of inflammation. We suggest early and continued monitoring of liver enzymes as they can be useful to identify patients who may need early escalation of care.

Internal Medicine

Shamaa O, **Jafri SM**, **Shamaa MT**, **Brown K**, and **Venkat D**. Takotsubo Cardiomyopathy Following Liver Transplantation: A Report of 2 Cases. *Transplant Proc* 2021; 53(1):239-243. PMID: 32980136. Full Text

Internal Medicine, Henry Ford Hospital, Detroit, Michigan, United States. Electronic address: Omaar10y@gmail.com.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan, United States.
General Surgery, Henry Ford Hospital, Detroit, Michigan, United States.

PURPOSE: Takotsubo cardiomyopathy, also called apical ballooning syndrome, is characterized by regional left ventricular systolic dysfunction that resembles myocardial infarction in its initial presentation; however, it lacks angiographic evidence of coronary artery disease. We evaluated the incidence of takotsubo cardiomyopathy following liver transplant at a diverse urban transplant program. METHODS: This is a retrospective review of patients transplanted at a single center between 2017 and 2019. Here we report 2 cases of takotsubo cardiomyopathy that developed after liver transplantation. RESULTS: A 65-year-old woman diagnosed with alcoholic cirrhosis underwent a brain-dead donor liver transplant. The postoperative course was complicated by stroke, pulmonary hypertension, and a left internal jugular thrombus. Six months following transplant, the patient developed takotsubo cardiomyopathy with congestive hepatopathy and died of heart failure complications despite maximal medical care. The second case was a 65-year-old woman with alcoholic cirrhosis admitted for a living donor liver transplant. The postoperative period involved recurrent seizures and elevated troponins with markedly reduced ejection fraction, which were appropriately managed. The patient recovered well with supportive care and was discharged to a rehabilitation facility shortly after. CONCLUSION: We present a series of patients with takotsubo cardiomyopathy after liver transplantation. The diagnosis depends on the clinical presentation and findings on electrocardiography, echocardiography, and cardiac enzymes. Our patients met the Mayo Clinic diagnostic criteria and were appropriately managed according to guidelines. Our report highlights the possibility of pulmonary hypertension contributing to the development of takotsubo cardiomyopathy. Additional studies are needed to establish a definite correlation.

Neurology

Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, Lee JW, Wusthoff CJ, Hahn CD, Westover MB, Gerard EE, Herman ST, Haider HA, **Osman G**, Rodriguez-Ruiz A, Maciel CB, Gilmore EJ, Fernandez A, Rosenthal ES, Claassen J, Husain AM, Yoo JY, So EL, Kaplan PW, Nuwer MR, van Putten M, Sutter R, Drislane FW, Trinka E, and Gaspard N. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J Clin Neurophysiol* 2021; 38(1):1-29. PMID: 33475321. Full Text

Comprehensive Epilepsy Center, Department of Neurology, Yale University School of Medicine, New Haven, Connecticut, U.S.A.
Westmead Comprehensive Epilepsy Unit, Westmead Hospital, University of Sydney, Sydney, Australia.
Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria.
Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, U.S.A.
Department of Clinical Neurophysiology, Danish Epilepsy Center, Dianalund and Aarhus University Hospital, Aarhus, Denmark.
Departments of Neurology and Pediatrics, The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.
Brigham and Women's Hospital, Boston, Massachusetts, U.S.A.
Division of Child Neurology, Stanford University, Palo Alto, California, U.S.A.
Division of Neurology, The Hospital for Sick Children, and Department of Pediatrics, University of Toronto, Toronto, Canada.
Neurology Department, Massachusetts General Hospital, Massachusetts, U.S.A.
Comprehensive Epilepsy Center, Department of Neurology, Northwestern University, Chicago, Illinois, U.S.A.
Barrow Neurological Institute, Phoenix, Arizona, U.S.A.
Department of Neurology, Henry Ford Hospital, Detroit, Michigan, U.S.A.
Division of Neurocritical Care, Department of Neurology, University of Florida, Gainesville, Florida, U.S.A.
Department of Neurology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, U.S.A.
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.
Neurocritical Care, Department of Neurology, Columbia University, New York, New York, U.S.A.
Department of Medicine (Neurology), Duke University Medical Center, and Veterans Affairs Medical Center, Durham, North Carolina, U.S.A.
Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, U.S.A.
Division of Epilepsy, Mayo Clinic, Rochester, Minnesota, U.S.A.
Department of Neurology, Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Center, Baltimore, Maryland, U.S.A.
Department of Neurology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California, U.S.A.
Medisch Spectrum Twente and University of Twente, Enschede, The Netherlands.
Medical Intensive Care Units and Department of Neurology, University Hospital Basel, Basel, Switzerland.
Department of Neurology, Harvard Medical School, and Comprehensive Epilepsy Center, Beth Israel Deaconess Medical Center, Boston, Massachusetts, U.S.A.; and.
Department of Neurology, Université Libre de Bruxelles, Hôpital Erasme, Brussels, Belgium.

Neurology

Memon AB, Al-Hader R, Patel S, Malik S, Megally M, Steijlen KL, Suri RR, and **Corrigan J**. Late-onset rapidly progressive MRI- negative-myelitis after COVID-19 illness. *Clin Neurol Neurosurg* 2021; 202:106513. PMID: 33517162. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA; Wayne State University, School of Medicine, Detroit, Michigan, USA. Electronic address: AMEMON2@hfhs.org.
Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Radiology, Henry Ford Hospital, Detroit, Michigan, USA; Wayne State University, School of Medicine, Detroit, Michigan, USA.

Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA; Wayne State University, School of Medicine, Detroit, Michigan, USA.

Neurology
Nour HA, **Miller DJ**, and **Danoun OA**. Naratriptan-Associated Spinal Artery Infarction. *Am J Ther* 2021; Epub ahead of print. PMID: 33491969. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, MI.

Neurology
Tahir RA, **Affan M**, **Marin H**, **Haider SA**, **Alsrouji OK**, **Ahmad A**, **Chebl AB**, **Katramados A**, **Van Harn M**, and **Kole M**. Quantification of pial collateral pressure in acute large vessel occlusion stroke: basic concept with patient outcomes. *Neuroradiology* 2021; Epub ahead of print. PMID: 33507337. Full Text

Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Radiology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Public Health Sciences, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mkole1@hfhs.org.
Department of Radiology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mkole1@hfhs.org.

PURPOSE: Pial collateral perfusion to the ischemic penumbra plays a critical role in determining patient outcomes in acute stroke. We aimed to assess the validity and reliability of an intra-procedural technique for measuring and quantifying the pial collateral pressure (QPCP) to ischemic brain tissue during acute stroke secondary to LVO. QPCP measurements were correlated with standard computed tomography angiography (CTA) and digital subtraction angiography imaging assessments of pial collateral perfusion and outcomes after mechanical endovascular revascularization (MER). METHODS: This prospective cohort study included 60 consecutive patients with middle cerebral artery (MCA)-M1 and proximal M2 occlusions. QPCP measurements were obtained during MER. The validity of QPCP measurements was evaluated using four widely accepted collateral grading scales. QPCP measurements were also analyzed as a predictor of patient outcomes utilizing National Institute of Health Stroke Scale reduction at 24 h and modified Rankin Scale (mRS) scores at 30 days. RESULTS: QPCP measurements and QPCP ratio (QPCP/systemic mean arterial blood pressure) showed a statistically significant association with single-phase pretreatment CTA Maas and American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology binary grading scales. Patient outcomes demonstrated for every 10-unit increase in QPCP, the odds of mRS 0-2 at 30 days increased by 76% ($p = 0.019$). CONCLUSION: QPCP measurements related best with the pretreatment CTA Maas collateral grading scale but were more strongly associated with patient outcomes than any of the four widely accepted collateral grading scales. Greater QPCP was significantly associated with better overall patient outcomes as defined by mRS at 30 days.

Neurology
Varelas PN, **Rehman M**, **Mehta C**, Louchart L, **Schultz L**, **Brady P**, **Kananeh MF**, and Wijdicks EFM. Comparison of 1 vs 2 Brain Death Examinations on Time to Death Pronouncement and Organ Donation: A 12-year Single Center Experience. *Neurology* 2021; Epub ahead of print. PMID: 33514644. Full Text

Department of Neurology, Henry Ford Hospital, Detroit MI, varelap@amc.edu.
Department of Neurology, Henry Ford Hospital, Detroit MI.
Gift of Life of MI, Ann Arbor, MI and Henry Ford Organ Transplant Center, Detroit, MI.
Department of Public Health Sciences, Henry Ford Hospital, Detroit MI.
Division of Neurocritical Care and Hospital Neurology, Mayo Clinic, Rochester, MN.

OBJECTIVE: To fill the evidence gap on the value of a single (SBD) or dual brain death (DBD) exam by providing data on irreversibility of brain function, organ donation consent and transplantation METHODS: 12-year tertiary hospital and organ procurement organization data on brain death (BD) were combined and outcomes, including consent rate for organ donation and organs recovered and transplanted after SBD and DBD were compared after multiple adjustments for co-variatesResults: two-hundred sixty-six patients were declared BD, 122 after SBD and 144 after DBD. Time from event to BD declaration was longer by an average of 20.9 hours after DBD (p=0.003). Seventy-five (73%) families of patients with SBD and 86 (72%) with DBD consented for organ donation (p=0.79). The number of BD exams was not a predictor for consent. No patient regained brain function during the periods following BD. Patients with SBD were more likely to have at least one lung transplanted (p = 0.033). The number of organs transplanted was associated with the number of exams [beta coefficient, (95% CI) -0.5 (-0.97 to -0.02), p=0.044], along with age (for 5 year increase, -0.36 (-0.43 to -0.29), p<0.001) and PaO(2) level (for 10 mmHg increase, 0.026 (0.008 to 0.044), p=0.005) and decreased as the elapsed time to BD declaration increased (p=0.019). CONCLUSIONS: A single neurologic examination to determine brain death is sufficient in patients with non-anoxic catastrophic brain injuries. A second examination is without additional yield in this group and its delay reduces the number of organs transplanted.

Neurology
Wasade VS, and **Logan JL**. Prolonged postictal hemianopsia after a focal extraoccipital onset seizure. *BMJ Case Rep* 2021; 14(1). PMID: 33431543. Full Text

Neurology, Henry Ford Medical Group, Detroit, Michigan, USA vwasade1@hfhs.org.
Neurology, Henry Ford Medical Group, Detroit, Michigan, USA.

We report a case of a prolonged postictal hemianopsia occurring after a focal extraoccipital seizure. A 55-year-old man with a history of neurosyphilis, treated with penicillin, presented to our epilepsy monitoring unit (EMU) for diagnostic evaluation of his spells occurring for 2 years. The spell semiology was stereotypical, described as oral and manual automatisms, speech difficulty and unresponsiveness. During the EMU stay, after his typical seizure was recorded, he experienced right hemianopsia lasting for 2 hours. Electrographically, the ictal pattern was prominent over the left temporal derivation and propagated to the left occipital derivation as the seizure progressed. Interictal epileptiform activity was over the left temporal derivations. We support the view that postictal phenomenon may represent merely a seizure termination zone and not be necessarily localising to the seizure onset zone. Furthermore, prolonged isolated postictal symptom of hemianopsia could also be noted in rare situations.

Neurology
Zahoor I, **Rui B**, **Khan J**, **Datta I**, and **Giri S**. An emerging potential of metabolomics in multiple sclerosis: a comprehensive overview. *Cell Mol Life Sci* 2021; Epub ahead of print. PMID: 33449145. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, MI, 48202, USA. izahoor1@hfhs.org.
Department of Neurology, Henry Ford Hospital, Education & Research Building, Room 4023, 2799 W Grand Blvd, Detroit, MI, 48202, USA. izahoor1@hfhs.org.
Department of Neurology, Henry Ford Hospital, Detroit, MI, 48202, USA.
Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, 48202, USA.
Department of Neurology, Henry Ford Hospital, Detroit, MI, 48202, USA. SGiri1@hfhs.org.
Department of Neurology, Henry Ford Hospital, Education & Research Building, Room 4051, 2799 W Grand Blvd, Detroit, MI, 48202, USA. SGiri1@hfhs.org.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the nervous system that primarily affects young adults. Although the exact etiology of the disease remains obscure, it is clear that alterations in the metabolome contribute to this process. As such, defining a reliable and disease-specific metabolome has tremendous potential as a diagnostic and therapeutic strategy for MS. Here, we provide an overview of studies aimed at identifying the role of metabolomics in MS. These offer new insights into disease pathophysiology and the contributions of metabolic pathways to this process, identify unique markers indicative of treatment responses, and demonstrate the therapeutic effects of drug-like

metabolites in cellular and animal models of MS. By and large, the commonly perturbed pathways in MS and its preclinical model include lipid metabolism involving alpha-linoleic acid pathway, nucleotide metabolism, amino acid metabolism, tricarboxylic acid cycle, D-ornithine and D-arginine pathways with collective role in signaling and energy supply. The metabolomics studies suggest that metabolic profiling of MS patient samples may uncover biomarkers that will advance our understanding of disease pathogenesis and progression, reduce delays and mistakes in diagnosis, monitor the course of disease, and detect better drug targets, all of which will improve early therapeutic interventions and improve evaluation of response to these treatments.

Neurosurgery

Donaldson K, Callahan KE, Gelinne A, Everett W, Ames SE, **Air EL**, and Durham SR. Gender diversity in United States neurosurgery training programs. *J Neurosurg* 2021; Epub ahead of print. PMID: 33513578. Full Text

1University of Vermont College of Medicine.
2Department of Neurosurgery, University of North Carolina, Chapel Hill, North Carolina.
3Department of Orthopaedics and Rehabilitation and.
4Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan; and.
5Division of Neurosurgery, University of Vermont College of Medicine, Burlington, Vermont.

OBJECTIVE: Neurosurgery continues to be one of the medical specialties with the lowest representation of females in both the resident and faculty workforce. Currently, there are limited available data on the gender distribution of faculty and residents in Accreditation Council for Graduate Medical Education (ACGME)-accredited neurosurgery training programs. This information is critical to accurately measure the results of any effort to improve both the recruitment and retention of women in neurosurgery. The objective of the current study was to define the current gender distribution of faculty and residents in ACGME-accredited neurosurgery training programs. METHODS: Data publicly available through institutional and supplemental websites for neurosurgical faculty and residents at ACGME-accredited programs were analyzed for the 2017-2018 academic year. Data collected for faculty included gender, age, year of residency graduation, academic rank, h-index, American Board of Neurological Surgery certification status, and leadership positions. Resident data included gender and postgraduate year of training. RESULTS: Among the 109 ACGME-accredited neurosurgical residency programs included in this study, there were 1350 residents in training, of whom 18.2% were female and 81.8% were male. There are 1320 faculty, of whom 8.7% were female and 91.3% were male. Fifty-eight programs (53.2%) had both female faculty and residents, 35 programs (32.1%) had female residents and no female faculty, 4 programs (3.7%) had female faculty and no female residents, and 6 programs (5.5%) lacked both female residents and faculty. Six programs (5.5%) had incomplete data. Female faculty were younger, had lower h-indices, and were less likely to be board certified and attain positions of higher academic rank and leadership. CONCLUSIONS: This study serves to provide a current snapshot of gender diversity in ACGME-accredited neurosurgery training programs. While there are still fewer female neurosurgeons achieving positions of higher academic rank and serving in leadership positions than male neurosurgeons, the authors' findings suggest that this is likely due to the small number of women in the neurosurgical field who are the farthest away from residency graduation and serves to highlight the significant progress that has been made toward achieving greater gender diversity in the neurosurgical workforce.

Neurosurgery

Massie L, Gunaseelan V, Waljee J, Brummett C, and **Schwalb JM**. Relationship between initial opioid prescription size and likelihood of refill after spine surgery. *Spine J* 2021; Epub ahead of print. PMID: 33460812. Full Text

Department of Neurosurgery, Duke University, 3480 Wake Forest Rd, Raleigh, NC 27609, USA. Michigan Opioid Prescribing Engagement Network (M-OPEN), 2800 Plymouth Rd, North Campus Research Complex (NCRC), Bldg 16, Ann Arbor, MI 48109, USA.

Michigan Opioid Prescribing Engagement Network (M-OPEN), 2800 Plymouth Rd, North Campus Research Complex (NCRC), Bldg 16, Ann Arbor, MI 48109, USA; Department of Surgery, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5048, USA.
Michigan Opioid Prescribing Engagement Network (M-OPEN), 2800 Plymouth Rd, North Campus Research Complex (NCRC), Bldg 16, Ann Arbor, MI 48109, USA; Department of Anesthesiology, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5048, USA.
Department of Neurosurgery, Henry Ford Medical Group, 2799 West Grand Blvd, K-11, Detroit, MI 48202, USA; Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI 48202, USA; Michigan Spine Surgery Improvement Collaborative (MSSIC), 1 Ford Place, 3A, Detroit, MI 48202, USA. Electronic address: jschwal1@hfhs.org.

BACKGROUND CONTEXT: Best practices in opioid prescribing after elective surgery have been developed for most surgical subspecialties, including spine. However, some percentage of patients will become chronic users. PURPOSE: This study aimed to determine the relationship between the size of initial opioid prescription after surgery for degenerative spinal disease and the likelihood of refills. STUDY DESIGN/SETTING: Retrospective case-control study. PATIENT SAMPLE: Opioid-naïve patients aged 18 to 64 undergoing elective spinal procedures (anterior cervical discectomy and fusion, posterior cervical fusion, lumbar decompression, and lumbar fusion) from 2010 to 2015 filling an initial perioperative prescription using insurance claims from Truven Health MarketScan (n=25,329). OUTCOME MEASURES: Functional measure: health-care utilization. Primary outcome was occurrence of an opioid refill within 30 postoperative days. METHODS: We used logistic regression to examine the probability of an additional refill by initial opioid prescription strength, adjusting for patient factors. RESULTS: About 26.3% of opioid-naïve patients obtained refills of their opioid prescriptions within 30 days of surgery. The likelihood of obtaining a refill was unchanged with the size of the initial perioperative prescription across procedure categories. Patient factors associated with increased likelihood of refills included age 30 to 39 years (odds ratio [OR] 1.137, p=.007, 95% confidence interval [CI] 1.072-1.249), female gender (OR 1.137, p<.001, 95% CI 1.072-1.207), anxiety disorder (OR 1.141, p=.017, 95% CI 1.024-1.272), mood disorder (OR 1.109 p=.049, 95% CI 1.000-1.229), and history of alcohol/substance abuse (OR 1.445 p=.006, 95% CI 1.110-1.880). CONCLUSIONS: For opioid-naïve patients, surgeons can prescribe lower amounts of opioids after elective surgery for degenerative spinal disease without concern of increased need for refills.

Neurosurgery

Nagaraja TN, and **Lee IY**. Cerebral microcirculation in glioblastoma: a major determinant of diagnosis, resection and drug delivery. *Microcirculation* 2021; Epub ahead of print. PMID: 33474805. Full Text

Dept. of Neurosurgery, Henry Ford Hospital, Detroit, MI, 48202, USA.

Glioblastoma (GBM) is the most common primary brain tumor with a dismal prognosis. Current standard of treatment is maximal, safe tumor resection followed by chemotherapy and radiation. Altered cerebral microcirculation and elevated blood-tumor barrier (BTB) permeability in tumor periphery due to glioma-induced vascular dysregulation allow T1 contrast-enhanced visualization of resectable tumor boundaries. Newer tracers that label the tumor and its vasculature are being increasingly used for intra-operative delineation of glioma boundaries for even more precise resection. Fluorescent 5-aminolevulinic acid (5-ALA) and indocyanine green (ICG) are examples of such intra-operative tracers. Recently, magnetic resonance imaging (MRI)-based MR thermometry is being employed for laser interstitial thermal therapy (LITT) for glioma debulking. However, aggressive, fatal recurrence always occurs. Post-surgical chemotherapy is hampered by the inability of most drugs to cross the blood-brain barrier (BBB). Understanding post-surgical changes in brain microcirculation and permeability is crucial to improve chemotherapy delivery. It is important to understand whether any microcirculatory indices can differentiate between true recurrence and radiation necrosis. LITT leads to peri-ablation BBB opening that persists for several weeks. Whether it can be a conduit for chemotherapy delivery is yet to be explored. This review will address the role of cerebral microcirculation in such emerging ideas in GBM diagnosis and therapy.

Neurosurgery

Tahir RA, **Affan M**, **Marin H**, **Haider SA**, **Alsrouji OK**, **Ahmad A**, **Chebl AB**, **Katramados A**, **Van Harn M**, and **Kole M**. Quantification of pial collateral pressure in acute large vessel occlusion stroke: basic concept with patient outcomes. *Neuroradiology* 2021; Epub ahead of print. PMID: 33507337. Full Text

Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Radiology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Public Health Sciences, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mkole1@hfhs.org.
Department of Radiology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mkole1@hfhs.org.

PURPOSE: Pial collateral perfusion to the ischemic penumbra plays a critical role in determining patient outcomes in acute stroke. We aimed to assess the validity and reliability of an intra-procedural technique for measuring and quantifying the pial collateral pressure (QPCP) to ischemic brain tissue during acute stroke secondary to LVO. QPCP measurements were correlated with standard computed tomography angiography (CTA) and digital subtraction angiography imaging assessments of pial collateral perfusion and outcomes after mechanical endovascular revascularization (MER). METHODS: This prospective cohort study included 60 consecutive patients with middle cerebral artery (MCA)-M1 and proximal M2 occlusions. QPCP measurements were obtained during MER. The validity of QPCP measurements was evaluated using four widely accepted collateral grading scales. QPCP measurements were also analyzed as a predictor of patient outcomes utilizing National Institute of Health Stroke Scale reduction at 24 h and modified Rankin Scale (mRS) scores at 30 days. RESULTS: QPCP measurements and QPCP ratio (QPCP/systemic mean arterial blood pressure) showed a statistically significant association with single-phase pretreatment CTA Maas and American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology binary grading scales. Patient outcomes demonstrated for every 10-unit increase in QPCP, the odds of mRS 0-2 at 30 days increased by 76% ($p = 0.019$). CONCLUSION: QPCP measurements related best with the pretreatment CTA Maas collateral grading scale but were more strongly associated with patient outcomes than any of the four widely accepted collateral grading scales. Greater QPCP was significantly associated with better overall patient outcomes as defined by mRS at 30 days.

Orthopaedics/Bone and Joint Center

Grushky AD, **Im SJ**, Steenburg SD, and Chong S. Traumatic Injuries of the Foot and Ankle. *Semin Roentgenol* 2021; 56(1):47-69. PMID: 33422183. Full Text

Division of Emergency Radiology, Department of Radiology, University of Michigan, Ann Arbor, MI. Electronic address: algrushk@med.umich.edu.
Department of Sports Medicine, Henry Ford Hospital, Detroit, MI.
Department of Radiology and Imaging Sciences, Indiana University School of Medicine and Indiana University Health, Indianapolis, IN.
Emergency Radiology Division, Department of Radiology and Imaging Sciences, Indiana University School of Medicine and Indiana University Health, Indianapolis, IN.

Orthopaedics/Bone and Joint Center

Guo EW, **Elhage K**, **Cross AG**, **Hessburg L**, **Gulledge CM**, Mehta N, Verma NN, and **Makhni EC**. Establishing and comparing reference preoperative Patient-Reported Outcomes Measurement Information System (PROMIS) scores in patients undergoing shoulder surgery. *J Shoulder Elbow Surg* 2020; Epub ahead of print. PMID: 33010435. Full Text

Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, MI, USA.
Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA.

Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, MI, USA. Electronic address: ericmakhnimd@gmail.com.

BACKGROUND: The Patient-Reported Outcomes Measurement Information System (PROMIS) has become increasingly popular among orthopedic surgeons treating shoulder pathology. Despite this, there have been few studies that have described and compared preoperative reference scores for specific shoulder surgical procedures. The primary purpose of this study was to establish and compare baseline preoperative PROMIS scores for 3 common types of shoulder surgery: rotator cuff repair (RCR), total shoulder arthroplasty (TSA), and labral repair (LR). The secondary goal was to stratify these operative groups by diagnosis and compare preoperative PROMIS scores. METHODS: In this cross-sectional study, adult and pediatric patients who underwent surgery for either RCR, TSA, or LR were included. PROMIS-Upper Extremity (UE), PROMIS-Pain Interference (PI), and PROMIS-Depression (D) scores that were collected at each patient's preoperative visit were reviewed. Continuous and categorical variables were compared between operative groups using analysis of variance and $\chi(2)$ or Fisher exact tests, respectively. Multivariable general linear models were used to identify significant independent predictors of PROMIS scores when controlling for age, sex, and body mass index. RESULTS: A total of 413 patients were included in the study: 272 in the RCR group, 84 in the TSA group, and 57 in the LR group. The average PROMIS-UE score was 39.8 in the LR group vs. 29.9 in the RCR group ($P < .001$) and 29.6 in the TSA group ($P < .001$). There was no difference between the mean RCR and TSA PROMIS-UE scores ($P = .93$). The average PROMIS-PI score was 56.6 in the LR group vs. 62.8 in the RCR group ($P < .001$) and 63.9 in the TSA group ($P < .001$). There was no difference between RCR and TSA PROMIS-PI scores ($P = .09$). The average PROMIS-D score was 43.5 in the LR group vs. 47.7 in the RCR group ($P = .004$) and 50.3 in the TSA group ($P < .001$). The TSA group had a higher mean PROMIS-D score than the RCR group ($P = .03$). For PROMIS-UE scores, age and body mass index were not found to be significant independent predictors ($P = .98$ and $P = .88$, respectively). For PROMIS-PI scores, age, body mass index, and sex were not found to be significant independent predictors ($P = .31$, $P = .81$, and $P = .48$, respectively). CONCLUSION: Patients undergoing shoulder LR had higher preoperative function scores and lower pain interference and depression scores than those undergoing TSA and RCR. These baseline PROMIS scores should be taken into consideration when tracking a patient's outcomes after surgery, as a certain score could mean drastically different functional and pain outcomes depending on the underlying pathology.

Orthopaedics/Bone and Joint Center

Jildeh TR, **Abbas MJ**, **Buckley P**, and **Okoroha KR**. The Use of Biologics for Hip Preservation. *Curr Rev Musculoskelet Med* 2021; Epub ahead of print. PMID: 33483876. Full Text

Department of Orthopaedic Surgery, Henry Ford Health System, 2799 W. Grand Blvd, Detroit, MI, 48202, USA. touficjildeh@gmail.com.
Department of Orthopaedic Surgery, Henry Ford Health System, 2799 W. Grand Blvd, Detroit, MI, 48202, USA.

PURPOSE OF REVIEW: A wide array of nonoperative modalities to treat hip pain are aimed at restoring and maintaining the structural and physiologic characteristics of the joint. The purpose of this review is to describe the current understanding of biologics in hip pathology by providing an evidence-based overview of treatment modalities available for orthopedic surgeons. RECENT FINDINGS: The use of biologics as a primary treatment or adjunct to traditional management has shown encouraging results for the treatment of hip pain. Studies have demonstrated safety with minimal complications when using platelet rich plasma, hyaluronic acid, or stem cells to treat hip pain caused by osteoarthritis, femoroacetabular impingement syndrome, tendinopathy, or osteonecrosis of the femoral head. Several studies have been able to demonstrate meaningful clinical results that can improve treatment standards for hip pain; however, more work must be performed to better delineate the appropriate protocols, indications, and limitations of each modality. Recent advances have inspired renewed interest in biologics for patients with hip pain. We present a concise review of platelet rich plasma, hyaluronic acid, stem cells, and matrix metalloprotease inhibitors and their applicability to hip preservation surgery.

Orthopaedics/Bone and Joint Center

Khalil LS, **Jildeh TR**, **Abbas MJ**, McIntosh MJ, Sokoli A, Cominos N, and **Okoroha KR**. Career Longevity and Performance Following Shoulder Instability in National Football League Athletes. *Arthroscopy* 2021; Epub ahead of print. PMID: 33422614. Full Text

Henry Ford Hospital, Department of Orthopaedic Surgery, 2799 W. Grand Blvd, Detroit, MI 48202. Electronic address: lskhalil@gmail.com.
Henry Ford Hospital, Department of Orthopaedic Surgery, 2799 W. Grand Blvd, Detroit, MI 48202.
Wayne State University School of Medicine, 540 E Canfield St, Detroit, MI 48201.
Michigan State University, College of Osteopathic Medicine, East Lansing, MI 48824.
Oakland University, Rochester, MI, 48309.

PURPOSE: To investigate the career longevity, game utilization and performance of National Football League (NFL) athletes following glenohumeral instability events treated operatively versus nonoperatively. METHODS: Public resources identified NFL players who sustained a shoulder instability event from 2000-2019. Players with prior shoulder instability, without NFL experience before injury, or who did not return to play (RTP) after injury were excluded. Demographic information, utilization (games and seasons), and season approximate value (SAV) statistics were recorded one year prior to injury and three years following return to play (RTP). Statistical analysis compared utilization and SAV following RTP for athletes managed operatively versus nonoperatively. RESULTS: Ninety-seven NFL players who sustained their first instability event while playing in the NFL were identified, 91 of whom RTP (93.8%). Quarterbacks were significantly more likely to undergo immediate surgical management compared to other positions (P=.023). Final analysis included 58 players managed operatively and 33 players managed nonoperatively by the end of the index season. Players treated operatively played in significantly more seasons following RTP during their remaining career (4.1±2.7 vs. 2.8±2.5 seasons; P=.015). There were no differences in games played or started, offensive or defensive snap count percentage, or performance (SAV) before and after injury when compared between cohorts (P>.05). Following surgical stabilization, time to RTP (36.62±10.32 vs. 5.43±12.33 weeks, P<.05) and time interval before recurrent instability (105.7±100.1 vs. 24.7±40.6 weeks, P<.001) were significantly longer than with non-operative treatment. Additionally, the operative cohort experienced less recurrent instability (27% vs. 50%; P=.035). CONCLUSIONS: Athletes who RTP in the NFL following a shoulder instability injury do so with similar workload and performance irrespective of surgical or non-surgical management. While nonoperative treatment is associated with faster return to play, operative management is associated with fewer recurrent instability events, greater time between recurrent instability events, and greater career longevity.

Orthopaedics/Bone and Joint Center

Klag EA, **Kuhlmann NA**, **Tramer JS**, **Franovic S**, and **Muh SJ**. Dexamethasone decreases postoperative opioid and antiemetic use in shoulder arthroplasty patients: A prospective, randomized controlled trial. *J Shoulder Elbow Surg* 2021; Epub ahead of print. PMID: 33486058. Full Text

Henry Ford Health System, Detroit, MI, USA.
Henry Ford Health System, Detroit, MI, USA. Electronic address: Smuh1@hfhs.org.

BACKGROUND: Multimodal pain control can be beneficial in relieving postoperative pain and limiting narcotic use following orthopedic procedures. Additionally, with increasing interest in outpatient arthroplasty procedures, providers have interest in adequate early postoperative pain control and complications. The purpose of this study was to investigate the effect of dexamethasone on pain, postoperative nausea and vomiting and length of stay following total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty (RTSA). METHODS: One-hundred and twelve patients undergoing TSA or RTSA by a single surgeon were assessed for inclusion in this investigation. We performed a prospective randomized, controlled trial to investigate the effect of 10mg of dexamethasone administered within 90 minutes of surgery. Primary outcome assessed was the average morphine equivalent use over the first 24 hours post-surgery. Secondary outcomes included postoperative visual analog scale (VAS) scores, anti-emetic use, postoperative nausea and vomiting and complications. RESULTS: A total of 75 patients were included in the final analysis with 32 patients (42.7%) randomized to the control group and

43 (57.3%) randomized to the dexamethasone group. Body mass index was significantly greater in the control group (33.8 vs 30.3, p=0.014), otherwise there were no significant demographic differences between groups. Average ondansetron use was significantly lower in the dexamethasone group compared to controls for the 0-4 hour interval (0.1 vs 0.9 mg, respectively, p=0.006) and was lower overall for the first 24 hours (0.3 vs 1.0 mg, p=0.025). Differences in VAS scores were significantly lower in the dexamethasone group at all time points (p<0.05 for all). The average VAS score over the 24-hour period for the dexamethasone group was also significantly lower than the controls (3 vs 6, p<0.001). Morphine equivalent use was significantly lower in the dexamethasone group compared to controls at 12-16 hours (1.7 vs 4.0 mg, respectively, p=0.004) and at 16-20 hours (1.7 vs 3.4 mg, respectively, p=0.006). When averaged over the first 24 hours, morphine equivalent was also significantly lower in the dexamethasone group (16.1 vs 25.4 mg, p=0.007). There was no significant difference in glucose control or complications between groups. CONCLUSION: Dexamethasone decreases opioid requirements in the first 24 hours following surgery, provides improved pain control, and decreases antiemetic use following shoulder arthroplasty. Dexamethasone is an important multimodal adjunct for controlling pain and postoperative nausea and vomiting following primary total shoulder arthroplasty.

Otolaryngology – Head and Neck Surgery
Craig JR, Saibene AM, and Felisati G. Chronic Odontogenic Rhinosinusitis: Optimization of Surgical Treatment Indications. *Am J Rhinol Allergy* 2021; 35(1):142-143. PMID: 33334132. Full Text

Department of Otolaryngology- Head and Neck Surgery, Henry Ford Health System, Detroit, Michigan. San Paolo Hospital, University of Milan, Milan, Italy.

Otolaryngology – Head and Neck Surgery
Craig JR, Tataryn RW, Cha BY, **Bhargava P**, Pokorny A, Gray ST, Mattos JL, and Poetker DM. Diagnosing odontogenic sinusitis of endodontic origin: A multidisciplinary literature review. *Am J Otolaryngol* 2021; 42(3):102925. PMID: 33486208. Full Text

Henry Ford Health System, Department of Otolaryngology- Head and Neck Surgery, Detroit, MI, United States of America. Electronic address: jcraig1@hfhs.org.
Tataryn Endodontics, Spokane, WA, United States of America; Loma Linda University, Department of Endodontics, School of Dentistry, Loma Linda, CA, United States of America.
University of Connecticut, Division of Endodontology, School of Dental Medicine, Farmington, CT, United States of America.
Henry Ford Health System, Department of Internal Medicine, Division of Infectious Disease, Detroit, MI, United States of America.
Spokane ENT Clinic, Spokane, WA, United States of America; University of Washington, Department of Otolaryngology- Head and Neck Surgery, Seattle, WA, United States of America.
Harvard Medical School, Department of Otolaryngology- Head and Neck Surgery, Boston, MA, United States of America.
University of Virginia, Department of Otolaryngology- Head and Neck Surgery, Charlottesville, VA, United States of America.
Medical College of Wisconsin, Department of Otolaryngology- Head and Neck Surgery, Milwaukee, WI, United States of America; Zablocki VAMC, Division of Surgery, Milwaukee, WI, United States of America.

PURPOSE: Endodontic disease is one of the most common causes of bacterial odontogenic sinusitis (ODS). Diagnosing ODS of endodontic origin involves otolaryngologists confirming sinusitis, and dental specialists confirming endodontic sources. The purpose of this study was to conduct a multidisciplinary literature review to highlight clinical and microbiological features of ODS, and the most optimal diagnostic modalities to confirm endodontic disease. METHODS: An extensive review of both medical and dental literature was performed by rhinologists, endodontists, and an infectious disease specialist. Frequencies of various clinical and microbiological features from ODS studies were collected, and averages were calculated. Different endodontic testing and imaging modalities were also evaluated on their abilities to confirm endodontic disease. RESULTS: ODS patients most often present with unilateral sinonasal symptoms for over 3 months, purulence on nasal endoscopy, and overt dental pathology on computed tomography (CT). Subjective foul smell, and maxillary sinus cultures demonstrating anaerobes and α-

streptococci (viridans group) may be more specific to ODS. For endodontic evaluations, cold pulp testing and cone-beam CT imaging are most optimal for confirming pulpal and periapical disease. CONCLUSION: Diagnosing ODS requires collaboration between otolaryngologists and dental specialists. Clinicians should suspect ODS when patients present with unilateral sinonasal symptoms, especially foul smell. Patients will generally have purulent drainage on nasal endoscopy, and both sinus opacification and overt dental pathology on CT. However, some patients will have subtle or absent dental pathology on CT. For suspected endodontic disease, endodontists should be consulted for at least cold pulp testing, and ideally cone-beam CT.

Otolaryngology – Head and Neck Surgery

Darrat I, **Tam S**, **Boulis M**, and **Williams AM**. Socioeconomic Disparities in Patient Use of Telehealth During the Coronavirus Disease 2019 Surge. *JAMA Otolaryngol Head Neck Surg* 2021; Epub ahead of print. PMID: 33443539. Full Text

Department of Otolaryngology-Head & Neck Surgery, Henry Ford Hospital, Detroit, Michigan.

IMPORTANCE: The coronavirus disease 2019 (COVID-19) pandemic required the rapid transition to telehealth with the aim of providing patients with medical access and supporting clinicians while abiding by the stay-at-home orders. OBJECTIVE: To assess demographic and socioeconomic factors associated with patient participation in telehealth during the COVID-19 pandemic. DESIGN, SETTING, AND PARTICIPANTS: This cohort study included all pediatric and adult patient encounters at the Department of Otolaryngology-Head & Neck Surgery in a tertiary care, academic, multisubspecialty, multisite practice located in an early hot spot for the COVID-19 pandemic from March 17 to May 1, 2020. Encounters included completed synchronous virtual, telephone, and in-person visits as well as visit no-shows. MAIN OUTCOMES AND MEASURES: Patient demographic characteristics, insurance status, and 2010 Census block level data as a proxy for socioeconomic status were extracted. Univariate and multivariate logistic regression models were created for patient-level comparisons. RESULTS: Of the 1162 patients (604 females [52.0%]; median age, 55 [range, 0-97] years) included, 990 completed visits; of these, 437 (44.1%) completed a virtual visit. After multivariate adjustment, females (odds ratio [OR], 1.71; 95% CI, 1.11-2.63) and patients with preferred provider organization insurance (OR, 2.70; 95% CI, 1.40-5.20) were more likely to complete a virtual visit compared with a telephone visit. Increasing age (OR per year, 0.98; 95% CI, 0.98-0.99) and being in the lowest median household income quartile (OR, 0.60; 95% CI, 0.42-0.86) were associated with lower odds of completing a virtual visit overall. Those patients within the second (OR, 0.53; 95% CI, 0.28-0.99) and lowest (OR, 0.33; 95% CI, 0.17-0.62) quartiles of median household income by census block and those with Medicaid, no insurance, or other public insurance (OR, 0.47; 95% CI, 0.23-0.94) were more likely to complete a telephone visit. Finally, being within the lower 2 quartiles of proportion being married (OR for third quartile, 0.49 [95% CI, 0.29-0.86]; OR for lowest quartile, 0.39 [95% CI, 0.23-0.67]) was associated with higher likelihood of a no-show visit. CONCLUSIONS AND RELEVANCE: These findings suggest that age, sex, median household income, insurance status, and marital status are associated with patient participation in telehealth. These findings identify vulnerable patient populations who may not engage with telehealth, yet still require medical care in a changing health care delivery landscape.

Otolaryngology – Head and Neck Surgery

Dunn R, **Marget MJ**, **Momin S**, and **Garcia-Rodriguez L**. Recurrent malignant peripheral nerve sheath tumor of the parietal scalp. *Am J Otolaryngol* 2021; 42(1):102812. PMID: 33130533. Full Text

Wayne State University School of Medicine, 540 E. Canfield Avenue, Detroit, MI 48201, United States of America. Electronic address: rtd@med.wayne.edu.
Department of Otolaryngology-Head & Neck Surgery, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI 48202, United States of America.

Malignant peripheral nerve sheath tumors (MPNSTs) are a rare and aggressive subtype of sarcomas defined by their neural origin. Head and neck manifestations are particularly uncommon. Challenges exist in diagnosis, management, and recurrence. Achieving local control, particularly in the head and neck region, is difficult. We present a patient with a rapidly enlarging MPNST on the right parietal calvarium

shortly after resection of a right vagus nerve MPNST. Recommendation was made for excision and reconstruction with a local advancement flap followed by radiation therapy. Local control with good aesthetic outcome was achieved by applying recommended surgical and oncologic principles.

Otolaryngology – Head and Neck Surgery
Freedman RL, **Sibley H**, **Williams AM**, and **Chang SS**. Race, not socioeconomic disparities, correlates with survival in human papillomavirus-negative oropharyngeal cancer: A retrospective study. *Am J Otolaryngol* 2021; 42(1):102816. PMID: 33161259. Full Text

Wayne State University School of Medicine, 540 E Canfield St, Detroit, MI 48201, USA; Kresge Eye Institute, 4717 Saint Antoine St., Detroit, MI 48201, USA; Ascension Providence Hospital, Southfield Campus, 16001 W 9 Mile Rd, Southfield, MI 48075, USA. Electronic address: ryfreedm@med.wayne.edu.
Department of Otolaryngology-Head and Neck Surgery, K8, Henry Ford Hospital, 2799 W Grand Blvd., Detroit, MI 48202, USA. Electronic address: hsibley1@hfhs.org.
Department of Otolaryngology-Head and Neck Surgery, K8, Henry Ford Hospital, 2799 W Grand Blvd., Detroit, MI 48202, USA. Electronic address: awilli50@hfhs.org.
Department of Otolaryngology-Head and Neck Surgery, K8, Henry Ford Hospital, 2799 W Grand Blvd., Detroit, MI 48202, USA. Electronic address: schang1@hfhs.org.

PURPOSE: Investigate the impact of black versus white race, socioeconomic status (SES), and comorbidity burden on oropharyngeal cancer (OPC) survival. MATERIALS AND METHODS: This study retrospectively analyzed patients diagnosed between 1991 and 2012 at an urban tertiary care center with a high volume of head and neck cancer referrals. Data gathered included demographics, human papilloma virus (HPV) status, follow-up time, comorbidities, smoking history, and overall survival. SES was extrapolated from the 2000 and 2010 censuses. Analysis of variance, chi-square tests, multivariable Cox proportional hazards models, Cox proportional hazards regression, Kaplan Meier curves and the log-rank test were utilized. RESULTS: Of 208 charts reviewed, 192 patients met inclusion criteria. Black patients had significantly ($p < 0.001$) poorer survival at 1, 2, and 5 years than white patients (5-year survival: 32% vs 64%); this discrepancy persisted in only HPV-negative disease (20% vs 50%). In the HPV-negative subgroup, there was no racial difference in treatment modality received, Charlson Comorbidity Index, and proportion receiving inadequate, noncurative or no treatment. Univariate analysis identified significant differences in median household income, education level, and stage at presentation between black and white subgroups. Multivariate analysis identified white race and HPV-positive status as independent predictors of overall survival, but SES and stage at presentation were not. CONCLUSION: SES did not explain the greater survival in HPV-negative white versus black patients. This indicates that race is an independent predictor of survival; future studies should examine more accurate indicators of SES and genetic differences in tumors of black and white patients.

Otolaryngology – Head and Neck Surgery
Grewal JS, Yanik SC, Strohl-Bryan AM, and Tatum SA. The unilateral cleft lip repair. *Am J Otolaryngol* 2021; 42(3):102908. PMID: 33508593. Full Text

Henry Ford Hospital, Department of Otolaryngology-Head & Neck Surgery, United States of America. Electronic address: jgrewal1@hfhs.org.
SUNY Upstate Medical University, Department of Otolaryngology and Communication Sciences, United States of America.
University of Rochester Medical Center, Department of Otolaryngology, United States of America.

OBJECTIVE: To determine if there is a benefit of 2-stage cleft lip repair in regard to improving facial symmetry and facilitating definitive lip, nose, and palate repair. STUDY DESIGN: Retrospective chart review of patients born with complete, unilateral cleft lip deformity that underwent a two-stage repair described as a stage 1 straight line repair and a stage 2 modified Millard repair, for which a complete set of records, and peri-operative and post-operative photos were available. All cases were performed by a single surgeon. SETTING: Tertiary care center craniofacial team. METHODS: Measurements were taken from intraoperative, perioperative, and postoperative images of patients before and after each stage. Ratios were then created comparing the affected size to the unaffected side, and these were averaged

between observers. RESULTS: A 19% increase in the width of area of the presumptive C flap was obtained between the unrepaired and the post-stage I images. The nostril width of the cleft side was 1.2× the width of the unaffected side, demonstrating a 140% decrease in nostril width at the completion of stage II. The cleft side nostril width was maintained slightly larger than the noncleft side as desired. Symmetry of the upper lip length was achieved, as the length of the cleft side lateral lip after stage II was 92% of the unaffected side. CONCLUSION: We believe this study provides evidence for our observations that a two-stage repair can be performed with functionally and aesthetically pleasing outcomes as an alternative to presurgical nasoalveolar molding.

Otolaryngology – Head and Neck Surgery

Zhong C, Xu L, Peng HL, **Tam S**, Xu L, Dahlstrom KR, Wu CF, Fu S, Chan W, Sturgis EM, Ramondetta LM, Rong L, Lairson DR, and Miao H. An economic and disease transmission model of human papillomavirus and oropharyngeal cancer in Texas. *Sci Rep* 2021; 11(1):1802. PMID: 33469199. Full Text

Department of Biostatistics and Data Science, School of Public Health, The University of Texas Health Science Center at Houston, 1200 Pressler Street, Houston, TX, 77030, USA.
Department of Statistics, School of Mathematical and Statistics, Guangdong University of Foreign Studies, Xiaoguwei Street, Guangzhou, Guangdong, China.
Department of Management, Policy, and Community Health, School of Public Health, The University of Texas Health Science Center at Houston, 1200 Pressler Street, Houston, TX, USA.
Department of Otolaryngology, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI, USA.
Department of Head and Neck Surgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX, USA.
Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, 1200 Pressler Street, Houston, TX, USA.
Division of Cancer Prevention and Population Sciences, Department of Epidemiology, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Houston, TX, USA.
Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX, USA.
Department of Mathematics, University of Florida, 1400 Stadium Rd, Gainesville, FL, USA.
Department of Biostatistics and Data Science, School of Public Health, The University of Texas Health Science Center at Houston, 1200 Pressler Street, Houston, TX, 77030, USA. Hongyu.Miao@uth.tmc.edu.

In 2017, 46,157 and 3,127 new oropharyngeal cancer (OPC) cases were reported in the U.S. and Texas, respectively. About 70% of OPC were attributed to human papillomavirus (HPV). However, only 51% of U.S. and 43.5% of Texas adolescents have completed the HPV vaccine series. Therefore, modeling the demographic dynamics and transmission of HPV and OPC progression is needed for accurate estimation of the economic and epidemiological impacts of HPV vaccine in a geographic area. An age-structured population dynamic model was developed for the U.S. state of Texas. With Texas-specific model parameters calibrated, this model described the dynamics of HPV-associated OPC in Texas. Parameters for the Year 2010 were used as the initial values, and the prediction for Year 2012 was compared with the real age-specific incidence rates in 23 age groups for model validation. The validated model was applied to predict 100-year age-adjusted incidence rates. The public health benefits of HPV vaccine uptake were evaluated by computer simulation. Compared with current vaccination program, increasing vaccine uptake rates by 50% would decrease the cumulative cases by 4403, within 100 years. The incremental cost-effectiveness ratio of this strategy was $94,518 per quality-adjusted life year (QALY) gained. Increasing the vaccine uptake rate by 50% can: (i) reduce the incidence rates of OPC among both males and females; (ii) improve the quality-adjusted life years for both males and females; (iii) be cost-effective and has the potential to provide tremendous public health benefits in Texas.

Pathology and Laboratory Medicine

Al-Obaidy KI, **Williamson SR**, Shelman N, Idrees MT, and Ulbright TM. Hepatoid Teratoma, Hepatoid Yolk Sac Tumor, and Hepatocellular Carcinoma: A Morphologic and Immunohistochemical Study of 30 Cases. *Am J Surg Pathol* 2021; 45(1):127-136. PMID: 32991342. Full Text

Department of Pathology & Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN.

Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI.

Rare hepatoid teratomas (HTs) in testicular germ cell tumor patients mimic hepatoid yolk sac tumor (HYST) and hepatocellular carcinoma (HCC). We compared the features of 2 metastatic HTs, 12 HYSTs, and 16 HCCs. The mean ages were 36, 40, and 62.5 years, respectively. The HTs formed sheets of hepatocyte-like cells with macrovesicular fat arranged in vague lobules with intervening fibrous bands containing biliary ductule-like structures and abortive portal triads. HTs lacked basement membrane deposits, with hepatoid cells staining for glypican-3, arginase, and HepPar-1 (2/2), whereas stains for CK19 (2/2) and CK7 (1/2) highlighted ductules and for villin hepatoid cells and ductules (1/2). SALL4 and CDX2 stains were negative (0/2). HYSTs formed nests, trabeculae, cords, and occasional gland-like structures, and most (10/12; 83%) produced intercellular basement membrane. No Mallory-Denk bodies were seen. Stains for SALL4 (100%), glypican-3 (100%), CK19 (88%), CDX2 (88%), and villin (75%) were positive, whereas those for HepPar-1 highlighted rare tumor cells (70%) and for arginase were mostly negative (26%). All HCCs lacked basement membrane deposits, with Mallory-Denk bodies occurring in 50%. Stains for HepPar-1 (100%) and arginase (94%) were positive, glypican-3 infrequent (19%), and SALL4, CK19, villin, and CDX2 negative. In summary, HTs are distinguished from HYST by the formation of ductules and abortive portal tracts, lack of basement membrane deposits, more consistent staining for arginase and HepPar-1, and negativity for SALL4 and CDX2. Contrasting features of HCCs with HYSTs include negativity for SALL4, CK19, and CDX2, frequent Mallory-Denk bodies, and absence of basement membrane deposits.

Pathology and Laboratory Medicine

Alhamar M, **Alkamachi B**, **Mehrotra H**, **Sanchez J**, **Ali H**, **Schultz D**, and **Chitale DA**. Clinical significance of quantitative categorization of HER2 fluorescent in situ hybridization results in invasive breast cancer patients treated with HER2-targeted agents. *Mod Pathol* 2021; Epub ahead of print. PMID: 33479447. Full Text

Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI, USA.
Department of Hematology and Medical Oncology, Henry Ford Health System, Detroit, MI, USA.
Department of Pathology and Laboratory Medicine, Henry Ford Health System, Detroit, MI, USA. DCHITAL1@hfhs.org.
Department of Pathology, Wayne State University School of Medicine, Detroit, MI, USA. DCHITAL1@hfhs.org.

HER2 (ERBB2) gene status serves as a strong predictive marker of response to HER2-targeted agents in invasive breast cancers, albeit with heterogeneous response. Our aim was to determine the distribution and prognosis of HER2 groups by fluorescent in situ hybridization (FISH) using the updated 2018 American Society of Clinical Oncology-College of American Pathologist (ASCO-CAP) guidelines. We identified 226 cases of equivocal or positive HER2 FISH invasive breast cancer (interpreted by ASCO-CAP guidelines at the time of reporting) who received HER2-targeted agents from 2006 to 2017. We subcategorized Group 1 further into three subgroups: low amplified (HER2/CEP17 ratio ≥ 2.0-2.99, mean HER2/cell 4.0-5.9), amplified (HER2/CEP17 ratio ≥ 2.0-2.99, mean HER2/cell ≥ 6), and excessive amplification (HER2/CEP17 ratio ≥ 3.0, mean HER2/cell ≥ 4.0). Outcomes studied were recurrence, metastasis, second breast primary, disease-specific survival (DSS), and overall survival (OS). Univariate analysis showed that the five categories of HER2 FISH were significantly associated with OS ($p < 0.01$), specifically higher HER2 amplification was associated with fewer deaths. HER2 FISH status also statistically significantly relates to DFS ($p < 0.01$) and metastasis ($p = 0.01$) but not with recurrence or second breast primary in our study. Tumor type and HER2 ISH Groups are independent predictors for both OS and DFS in our cohort. The proposed Group 1 subcategories were significantly associated with OS ($p < 0.01$) and DFS ($p < 0.01$), excessive HER2 amplification was associated with longer median survival. The Cox regression models showed better survival outcomes for the excessive amplification subgroup than the low amplified subgroup, with OS (hazard ratio = 0.63, 95% CI 0.42-0.93) and DFS (HR = 0.55, 95% CI 0.37-0.83). We demonstrated that in HER2 FISH Group 1 patients, high HER2 amplification was significantly associated with longer OS and DFS; these patients seem to benefit more from HER2-targeted regimens. We recommend reporting these Group 1 subcategories when assessing HER2 FISH.

Pathology and Laboratory Medicine

Greene DN, Marzinke MA, **Winston-McPherson GN**, and Goldstein Z. The Journal of Applied Laboratory Medicine Special Issue on Health Disparities. *J Appl Lab Med* 2021; 6(1):1-2. PMID: 33438737. Full Text

University of Washington, Department of Laboratory Medicine and Pathology, Seattle WA Washington
Kaiser Permanente, Renton, WA.
Johns Hopkins Medicine, Departments of Medicine and Pathology, Baltimore, MD.
Henry Ford Health System, Detroit, MI.
Callen Lorde Community Health, NY, NY.

Pathology and Laboratory Medicine

Hommerding O, Allory Y, Argani P, Bismar TA, Bubendorf L, Canete-Portillo S, Chaux A, Chen YB, Cheng L, Cubilla AL, Egevad L, Gill AJ, Grignon DJ, Hartmann A, Hes O, Idrees MT, Kao CS, Knowles MA, Looijenga LHJ, Lotan TL, Pritchard CC, Rubin MA, Tomlins SA, Van der Kwast TH, Velazquez EF, Warrick JI, **Williamson SR**, and Kristiansen G. [Molecular pathology of urogenital tumors : Recommendations from the 2019 International Society of Urological Pathology (ISUP) Consensus Conference]. *Pathologe* 2021; Epub ahead of print. PMID: 33398501. Full Text

Institut für Pathologie, Universitätsklinikum Bonn, Venusberg-Campus 1, Gebäude 62, 53127, Bonn, Deutschland.
Department of Pathology, Institut Curie, Saint-Cloud, Frankreich.
Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, USA.
Department of Pathology and Laboratory Medicine, University of Calgary Cumming School of Medicine and Alberta Public Labs, Calgary, Kanada.
Institut für Medizinische Genetik und Pathologie, Universitätsspital Basel, Basel, Schweiz.
Pathology and Research Institute, National University of Asuncion, Asunción, Paraguay.
Department of Scientific Research, Norte University, Asunción, Paraguay.
Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA.
Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, USA.
Pathology and Research Institute and Medical Sciences of National University of Asuncion, Asunción, Paraguay.
Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Schweden.
Department of Anatomical Pathology, NSW Health Pathology, Sidney, Australien.
Cancer Diagnosis and Pathology Research Group, Kolling Institute of Medical Research, Royal North Shore Hospital, St. Leonards, Australien.
Sydney Medical School, University of Sydney, Sydney, Australien.
Department of Pathology, Indiana University School of Medicine, Indianapolis, USA.
Institut für Pathologie, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Deutschland.
Medical Faculty and Charles University Hospital Plzen, Charles University, Pilsen, Tschechien.
Pathology, Indiana University School of Medicine, Indianapolis, USA.
Department of Pathology, Stanford University School of Medicine, Stanford, USA.
Divison of Molecular Medicine, Leeds Institute of Molecular Research at St James's, St James's University Hospital, Leeds, Großbritannien.
Princess Máxima Center for Pediatric Oncology, Utrecht, Niederlande.
Departments of Pathology, Oncology and Urology, Johns Hopkins University, Baltimore, USA.
Department of Laboratory Medicine, University of Washington, Seattle, USA.
Department for Biomedical Research, University of Bern and Bern Center for Precision Medicine, Bern, Schweiz.
Department of Pathology, Urology and Rogel Cancer Center, University of Michigan Medical School, Ann Arbor, USA.
Laboratory Medicine Program, University Health Network; Princess Margaret Cancer Centre, University of Toronto, Toronto, Kanada.
Inform Diagnostics and Tufts University, Boston, USA.

Department of Pathology, Penn State College of Medicine, Hershey, USA.
Department of Pathology and Laboratory Medicine and Henry Ford Cancer Institute, Henry Ford Health System, Detroit, USA.
Department of Pathology, Wayne State University School of Medicine, Detroit, USA.
Institut für Pathologie, Universitätsklinikum Bonn, Venusberg-Campus 1, Gebäude 62, 53127, Bonn, Deutschland. glen.kristiansen@ukb.uni-bonn.de.

Comprehensive understanding of molecular principles in cancer and the diversification of oncological therapy promise individual therapeutic concepts, which have not yet found their way into urogenital cancer therapy. In March 2019 the International Society of Urogenital Pathology (ISUP) therefore held a consensus conference on recommendations for molecular diagnostics of genitourinary tumors, which were published in five separate manuscripts and are summarized in this article.In preparation for the conference, a comprehensive survey of current practices for molecular testing of urogenital tumors was carried out by members of the ISUP. At the conference, the results and the corresponding background information were presented by five working groups and recommendations for action for diagnostics were developed. An agreement between 66% of the conference participants was defined as consensus.

Pathology and Laboratory Medicine
Onwubiko IN, **Taneja K**, **Gupta N**, and **Mukherjee A**. Unusual Case of Progressive Multifocal Leukoencephalopathy in a Patient With Sjögren Syndrome. *Am J Forensic Med Pathol* 2021; Epub ahead of print. PMID: 33464755. Full Text

From the Henry Ford Health System, Detroit, MI.

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease caused by reactivation of John Cunningham virus affecting typically subcortical and periventricular white matter of immunocompromised hosts (human immunodeficiency virus infection, hematologic malignancies). Cerebral hemispheric white matter is most commonly affected by lytic infections, leading to progressive damage to oligodendrocytes in the central nervous system. Neuroimaging usually highlights scattered foci of white matter hypodensity not attributable to contrast enhancement or mass effect. In contrast, we present an unusual case of PML predominantly affecting cervical spinal cord and brainstem in an immunocompetent host. This is a rare subset of PML case that can occur in association with connective tissue disorders (Sjögren Syndrome in this case), systemic lupus erythematosus being the most common. Progressive multifocal leukoencephalopathy should be considered in the differential diagnosis of spinal cord or brainstem lesions, particularly in the patients with connective tissue disorders.

Pathology and Laboratory Medicine
Zia S, **Shaw B**, **Chapman S**, and **Friedman BJ**. An atypical chondroid syringoma with malignant degeneration: utility of comparative genomic hybridization in confirming the diagnosis. *J Cutan Pathol* 2021; Epub ahead of print. PMID: 33470448. Full Text

Department of Pathology and Laboratory Medicine, Henry Ford Hospital, Detroit, MI.
Department of Dermatology, Henry Ford Hospital, Detroit, MI.

Chondroid syringoma represents the cutaneous counterpart of mixed tumor (pleomorphic adenoma) of salivary glands. Definitive diagnosis is made on histopathology and is based on the presence of characteristic epithelial and stromal components. We report a case of an atypical chondroid syringoma arising on the extremity of an elderly male patient. Histomorphologic features of necrosis and cellular atypia raised suspicion for malignant degeneration, an exceptionally rare circumstance in this context. To further support the diagnosis of malignancy, array comparative genomic hybridization (aCGH) was performed from both low and higher grade areas of the tumor. Both regions demonstrated multiple copy number gains and losses, with additional loss of 17p(TP53), loss of 19p, and loss of heterozygosity (LOH) on16q demonstrated in the more atypical foci. To our knowledge, this is the first case description of malignant degeneration of a chondroid syringoma with correlative microarray analysis. The findings in this case may prove useful in confirming the diagnosis in future ambiguous cases.

Pediatrics

Coleman CM, **Alexander GL**, **Barone C**, **Bossick AS**, **Kassem Z**, **Lu M**, **Zhou Y**, and **Cassidy-Bushrow AE**. Influence of a One-Time Web-Based Provider Intervention on Patient-Reported Outcomes After the Well-Child Visit: A Feasibility Study. *J Patient Cent Res Rev* 2021; 8(1):48-57. PMID: 33511253. Full Text

Patient-Engaged Research Center, Department of Public Health Sciences, Henry Ford Health System, Detroit, MI.
Department of Pediatric Administration, Henry Ford Health System, Detroit, MI.

PURPOSE: Patient-centered care promotes positive health outcomes in pediatrics. We created a provider-focused intervention and implemented it in a pragmatic clustered randomized controlled trial to improve health-related quality of life (HRQOL) among pediatric patients. METHODS: A one-time (1-1.5-hour) webinar focusing on patient-centered care and motivational interviewing, using obesity screening as an example, was developed. Pediatric providers were recruited and randomized to either intervention (webinar) or control (usual care) arms. All well-child visits to these providers for a period of up to 5 months following webinar completion (or study enrollment for controls) were identified, and these family/patients were invited to complete a survey to assess HRQOL postvisit. Reported outcomes were compared between intervention and control participants using clustered t-tests, chi-squared tests and multiple linear regression models. RESULTS: We recruited 20 providers (10 intervention, 10 control) to the study; 469 parents/guardians and 235 eligible children seeing these providers completed the postvisit survey. Parents/guardians of 8-12-year-old children in the intervention group reported higher school functioning compared to controls (83.5 vs 75.8; P=0.023). There were no other differences in children's HRQOL between intervention and control groups. CONCLUSIONS: A one-time, web-based provider intervention is feasible to implement in pediatrics. Modest evidence, requiring further study, indicates that instructing providers on patient-centered care in the well-child visit may improve aspects of pediatric HRQOL (ie, school functioning) compared to usual care. However, this was a brief intervention, with multiple outcomes tested and no evaluation of pre- and postintervention provider knowledge, thus additional study is needed.

Pediatrics

McGrath E, Dalal D, Smitherman L, Marshall S, Youngman C, **Barone CJ**, Gray H, Rehman N, and Secord E. "Would you like a Flu Shot with your order?" - A COVID-19 Pandemic Drive-Through Response to Address Delayed Pediatric Immunization in Detroit, Michigan. *Infect Control Hosp Epidemiol* 2021; Epub ahead of print. PMID: 33397534. Full Text

Wayne State University School of Medicine, Department of Pediatrics, Detroit, Michigan.
Detroit Health Department, Detroit, Michigan.
Henry Ford Hospital, Department of Pediatrics, Detroit, Michigan.

Pharmacy

D'Mello RJ, Hsu CD, **Chaiworapongsa P**, and Chaiworapongsa T. Update on the Use of Intravenous Immunoglobulin in Pregnancy. *Neoreviews* 2021; 22(1):e7-e24. PMID: 33386311. Request Article

Department of Obstetrics and Gynecology, Detroit Medical Center, Detroit, MI.
Department of Obstetrics and Gynecology and.
Department of Physiology, Wayne State University School of Medicine, Detroit, MI.
Department of Pharmacy, Henry Ford Hospital, Detroit, MI.

Intravenous immunoglobulin (IVIG) was first administered to humans in the 1980s. The mechanism of action of IVIG is still a subject of debate but the pharmacokinetics have been well characterized, albeit outside of pregnancy. IVIG has been used in pregnancy to treat several nonobstetrical and obstetrical-related conditions. However, current evidence suggests that IVIG use during pregnancy can be recommended for 1) in utero diagnosis of neonatal alloimmune thrombocytopenia; 2) gestational alloimmune liver disease; 3) hemolytic disease of the fetus and newborn for early-onset severe

intrauterine disease; 4) antiphospholipid syndrome (APS) when refractory to or contraindicated to standard treatment, or in catastrophic antiphospholipid syndrome; and 5) immune thrombocytopenia when standard treatment is ineffective or rapid increase of platelet counts is needed. All recommendations are based on case series and cohort studies without randomized trials usually because of the rare prevalence of the conditions, the high incidence of adverse outcomes if left untreated, and ethical concerns. In contrast, IVIG therapy cannot be recommended for recurrent pregnancy loss, and the use of IVIG in subgroups of those with recurrent pregnancy loss requires further investigations. For non-obstetrical-related conditions, we recommend using IVIG as indicated for nonpregnant patients. In conclusion, the use of IVIG during pregnancy is an effective treatment in some obstetrical-related conditions with rare serious maternal side effects. However, the precise mechanisms of action and the long-term immunologic effects on the fetus and neonate are poorly understood and merit further investigations.

Public Health Sciences

Brawner CA, **Ehrman JK**, **Bole S**, **Kerrigan DJ**, **Parikh SS**, **Lewis BK**, **Gindi RM**, **Keteyian C**, **Abdul-Nour K**, and **Keteyian SJ**. Inverse Relationship of Maximal Exercise Capacity to Hospitalization Secondary to Coronavirus Disease 2019. *Mayo Clin Proc* 2021; 96(1):32-39. PMID: 33413833. Full Text

Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI. Electronic address: cbrawne1@hfhs.org.
Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI.
Public Health Sciences, Henry Ford Health System, Detroit, MI.
Population Health, Henry Ford Allegiance Health, Jackson, MI.

OBJECTIVE: To investigate the relationship between maximal exercise capacity measured before severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and hospitalization due to coronavirus disease 2019 (COVID-19). METHODS: We identified patients (≥18 years) who completed a clinically indicated exercise stress test between January 1, 2016, and February 29, 2020, and had a test for SARS-CoV-2 (ie, real-time reverse transcriptase polymerase chain reaction test) between February 29, 2020, and May 30, 2020. Maximal exercise capacity was quantified in metabolic equivalents of task (METs). Logistic regression was used to evaluate the likelihood that hospitalization secondary to COVID-19 is related to peak METs, with adjustment for 13 covariates previously identified as associated with higher risk for severe illness from COVID-19. RESULTS: We identified 246 patients (age, 59±12 years; 42% male; 75% black race) who had an exercise test and tested positive for SARS-CoV-2. Among these, 89 (36%) were hospitalized. Peak METs were significantly lower (P<.001) among patients who were hospitalized (6.7±2.8) compared with those not hospitalized (8.0±2.4). Peak METs were inversely associated with the likelihood of hospitalization in unadjusted (odds ratio, 0.83; 95% CI, 0.74-0.92) and adjusted models (odds ratio, 0.87; 95% CI, 0.76-0.99). CONCLUSION: Maximal exercise capacity is independently and inversely associated with the likelihood of hospitalization due to COVID-19. These data further support the important relationship between cardiorespiratory fitness and health outcomes. Future studies are needed to determine whether improving maximal exercise capacity is associated with lower risk of complications due to viral infections, such as COVID-19.

Public Health Sciences

Cassidy-Bushrow AE, **Baseer M**, **Kippen K**, **Levin AM**, **Li J**, **Loveless I**, **Poisson LM**, **Schultz L**, **Wegienka G**, **Zhou Y**, and **Johnson CC**. Social distancing during the COVID-19 pandemic: quantifying the practice in Michigan - a "hotspot state" early in the pandemic - using a volunteer-based online survey. *BMC Public Health* 2021; 21(1):245. PMID: 33514350. Full Text

Department of Public Health Sciences, Henry Ford Hospital, 1 Ford Place, 5C, Detroit, MI, 48202, USA. acassid1@hfhs.org.
Department of Public Health Sciences, Henry Ford Hospital, 1 Ford Place, 5C, Detroit, MI, 48202, USA.

BACKGROUND: Public Health policies related to social distancing efforts during the COVID-19 pandemic helped slow the infection rate. However, individual-level factors associated with social distancing are largely unknown. We sought to examine social distancing during the COVID-19 pandemic in Michigan, an

infection "hotspot" state in the United States early in the pandemic. METHODS: Two surveys were distributed to Michigan residents via email lists and social media following COVID-19 related state mandates in March; 45,691 adults responded to the first survey and 8512 to the second. Staying home ≥ 3 out of 5 previous days defined having more social distancing. Logistic regression models were used to examine potential factors associated with more social distancing. RESULTS: Most respondents were women (86% in Survey 1, 87% in Survey 2). In Survey 1, 63% reported more social distancing, increasing to 78% in Survey 2. Female sex and having someone (or self) sick in the home were consistently associated with higher social distancing, while increasing age was positively associated in Survey 1 but negatively associated in Survey 2. Most respondents felt social distancing policies were important (88% in Survey 1; 91% in Survey 2). CONCLUSIONS: Michiganders responding to the surveys were both practicing and supportive of social distancing. State-level executive orders positively impacted behaviors early in the COVID-19 pandemic in Michigan. Additional supports are needed to help vulnerable populations practice social distancing, including older individuals.

Public Health Sciences

Coleman CM, **Alexander GL**, **Barone C**, **Bossick AS**, **Kassem Z**, **Lu M**, **Zhou Y**, and **Cassidy-Bushrow AE**. Influence of a One-Time Web-Based Provider Intervention on Patient-Reported Outcomes After the Well-Child Visit: A Feasibility Study. *J Patient Cent Res Rev* 2021; 8(1):48-57. PMID: 33511253. Full Text

Patient-Engaged Research Center, Department of Public Health Sciences, Henry Ford Health System, Detroit, MI.
Department of Pediatric Administration, Henry Ford Health System, Detroit, MI.

PURPOSE: Patient-centered care promotes positive health outcomes in pediatrics. We created a provider-focused intervention and implemented it in a pragmatic clustered randomized controlled trial to improve health-related quality of life (HRQOL) among pediatric patients. METHODS: A one-time (1-1.5-hour) webinar focusing on patient-centered care and motivational interviewing, using obesity screening as an example, was developed. Pediatric providers were recruited and randomized to either intervention (webinar) or control (usual care) arms. All well-child visits to these providers for a period of up to 5 months following webinar completion (or study enrollment for controls) were identified, and these family/patients were invited to complete a survey to assess HRQOL postvisit. Reported outcomes were compared between intervention and control participants using clustered t-tests, chi-squared tests and multiple linear regression models. RESULTS: We recruited 20 providers (10 intervention, 10 control) to the study; 469 parents/guardians and 235 eligible children seeing these providers completed the postvisit survey. Parents/guardians of 8-12-year-old children in the intervention group reported higher school functioning compared to controls (83.5 vs 75.8; P=0.023). There were no other differences in children's HRQOL between intervention and control groups. CONCLUSIONS: A one-time, web-based provider intervention is feasible to implement in pediatrics. Modest evidence, requiring further study, indicates that instructing providers on patient-centered care in the well-child visit may improve aspects of pediatric HRQOL (ie, school functioning) compared to usual care. However, this was a brief intervention, with multiple outcomes tested and no evaluation of pre- and postintervention provider knowledge, thus additional study is needed.

Public Health Sciences

Conti DV, Darst BF, **Rybicki BA**, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. *Nat Genet* 2021; 53(1):65-75. PMID: 33398198. Full Text

Prostate cancer is a highly heritable disease with large disparities in incidence rates across ancestry populations. We conducted a multiancestry meta-analysis of prostate cancer genome-wide association studies (107,247 cases and 127,006 controls) and identified 86 new genetic risk variants independently associated with prostate cancer risk, bringing the total to 269 known risk variants. The top genetic risk score (GRS) decile was associated with odds ratios that ranged from 5.06 (95% confidence interval (CI), 4.84-5.29) for men of European ancestry to 3.74 (95% CI, 3.36-4.17) for men of African ancestry. Men of African ancestry were estimated to have a mean GRS that was 2.18-times higher (95% CI, 2.14-2.22),

and men of East Asian ancestry 0.73-times lower (95% CI, 0.71-0.76), than men of European ancestry. These findings support the role of germline variation contributing to population differences in prostate cancer risk, with the GRS offering an approach for personalized risk prediction.

Public Health Sciences

Janic B, **Brown SL**, Neff R, Liu F, Mao G, **Chen Y**, **Jackson L**, **Chetty IJ**, **Movsas B**, and **Wen N**. Therapeutic enhancement of radiation and immunomodulation by gold nanoparticles in triple negative breast cancer. *Cancer Biol Ther* 2021; Epub ahead of print. PMID: 33459132. Full Text

Radiation Oncology, Henry Ford Hospital , Detroit, Michigan, USA.
University of Notre Dame , South Bend, Indiana, USA.
Department of Chemical Engineering and Materials Science, Wayne State University , Detroit, Michigan, USA.
School of Chemical Engineering, Unsw Sydney , Kensington, Australia.
Department of Public Health Sciences, Henry Ford Hospital , Detroit, Michigan, USA.

Gold nanoparticles (AuNPs) have been shown to enhance cancer radiotherapy (RT) gain by localizing the absorption of radiation energy in the tumor while sparing surrounding normal tissue from radiation toxicity. Previously, we showed that AuNPs enhanced RT induced DNA damage and cytotoxicity in MCF7 breast cancer cells. Interestingly, we found that cancer cells exhibited a size-dependent AuNPs intracellular localization (4 nm preferentially in the cytoplasm and 14 nm in the nucleus). We extended those studies to an in vivo model and examined the AuNPs effects on RT cytotoxicity, survival and immunomodulation of tumor microenvironment (TME) in human triple negative breast cancer (TNBC) xenograft mouse model. We also explored the significance of nanoparticle size in these AuNPs' effects. Mice treated with RT and RT plus 4 nm or 14 nm AuNPs showed a significant tumor growth delay, compared to untreated animals, while dual RT plus AuNPs treatment exhibited additive effect compared to either RT or AuNPs treatment alone. Survival log-rank test showed significant RT enhancement with 14 nm AuNP alone; however, 4 nm AuNPs did not exhibit RT enhancement. Both sizes of AuNPs enhanced RT induced immunogenic cell death (ICD) that was coupled with significant macrophage infiltration in mice pretreated with 14 nm AuNPs. These results showing significant AuNP size-dependent RT enhancement, as evident by both tumor growth delay and overall survival, reveal additional underlying immunological mechanisms and provide a platform for studying RT multimodal approaches for TNBC that may be combined with immunotherapies, enhancing their effect.

Public Health Sciences

Keteyian SJ, **Grimshaw C**, **Brawner CA**, **Kerrigan DJ**, **Reasons L**, **Berry R**, **Peterson EL**, and **Ehrman JK**. A Comparison of Exercise Intensity in Hybrid Versus Standard Phase Two Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev* 2021; 41(1):19-22. PMID: 33351540. Full Text

Division of Cardiovascular Medicine (Drs Keteyian, Brawner, Kerrigan, and Ehrman, Ms Grimshaw and Reasons, and Mr Berry) and Department of Public Health Sciences (Dr Peterson), Henry Ford Health System, Detroit, Michigan.

PURPOSE: To compare exercise training intensity during standard cardiac rehabilitation (S-CR) versus hybrid-CR (combined clinic- and remote home-/community-based). METHODS: The iATTEND (improving ATTENDance to cardiac rehabilitation) trial is currently enrolling subjects and randomizing patients to S-CR versus hybrid-CR. This substudy involves the first 47 subjects who completed ≥18 CR sessions. Patients in S-CR completed all visits in a typical phase II clinic-based setting and patients in hybrid-CR completed up to 17 of their sessions remotely using telehealth (TH). Exercise training intensity in both CR settings is based on heart rate (HR) data from each CR session, expressed as percent HR reserve. RESULTS: Among patients in both study groups, there were no serious adverse events or falls that required hospitalization during or within 3 hr after completing a CR session. Expressed as a percentage of HR reserve, the overall mean exercise training intensities during both the S-CR sessions and the TH-CR sessions from hybrid-CR were not significantly different at 63 ± 12% and 65 ± 10%, respectively (P = .29). CONCLUSION: This study showed that hybrid-CR delivered using remote TH results in exercise training intensities that are not significantly different from S-CR.

Public Health Sciences

Liu X, Emami H, Nejad-Davarani SP, Morris E, **Schultz L**, Dong M, and C KG-H. Performance of deep learning synthetic CTs for MR-only brain radiation therapy. *J Appl Clin Med Phys* 2021; Epub ahead of print. PMID: 33410568. Full Text

Department of Medical Physics, Memorial Sloan Kettering Cancer Center, Middletown, NJ, USA.
Department of Computer Science, Wayne State University, Detroit, MI, USA.
Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA.
Department of Radiation Oncology, University of California-Los Angeles, Los Angeles, CA, USA.
Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA.
Department of Human Oncology, School of Medicine and Public Heath, University of Wisconsin - Madison, Madison, WI, USA.

PURPOSE: To evaluate the dosimetric and image-guided radiation therapy (IGRT) performance of a novel generative adversarial network (GAN) generated synthetic CT (synCT) in the brain and compare its performance for clinical use including conventional brain radiotherapy, cranial stereotactic radiosurgery (SRS), planar, and volumetric IGRT. METHODS AND MATERIALS: SynCT images for 12 brain cancer patients (6 SRS, 6 conventional) were generated from T1-weighted postgadolinium magnetic resonance (MR) images by applying a GAN model with a residual network (ResNet) generator and a convolutional neural network (CNN) with 5 convolutional layers as the discriminator that classified input images as real or synthetic. Following rigid registration, clinical structures and treatment plans derived from simulation CT (simCT) images were transferred to synCTs. Dose was recalculated for 15 simCT/synCT plan pairs using fixed monitor units. Two-dimensional (2D) gamma analysis (2%/2 mm, 1%/1 mm) was performed to compare dose distributions at isocenter. Dose-volume histogram (DVH) metrics (D(95%) , D(99%) , D(0.2cc,) and D(0.035cc)) were assessed for the targets and organ at risks (OARs). IGRT performance was evaluated via volumetric registration between cone beam CT (CBCT) to synCT/simCT and planar registration between KV images to synCT/simCT digital reconstructed radiographs (DRRs). RESULTS: Average gamma passing rates at 1%/1mm and 2%/2mm were 99.0 ± 1.5% and 99.9 ± 0.2%, respectively. Excellent agreement in DVH metrics was observed (mean difference ≤0.10 ± 0.04 Gy for targets, 0.13 ± 0.04 Gy for OARs). The population averaged mean difference in CBCT-synCT registrations were <0.2 mm and 0.1 degree different from simCT-based registrations. The mean difference between kV-synCT DRR and kV-simCT DRR registrations was <0.5 mm with no statistically significant differences observed (P > 0.05). An outlier with a large resection cavity exhibited the worst-case scenario. CONCLUSION: Brain GAN synCTs demonstrated excellent performance for dosimetric and IGRT endpoints, offering potential use in high precision brain cancer therapy.

Public Health Sciences

Mishra K, **Naffouj S**, **Gorgis S**, **Ibrahim H**, **Gill S**, **Fadel R**, **Chatfield A**, **Tang A**, and **Salgia R**. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. *Hepatol Commun* 2021; 5(1):24-32. PMID: 33437898. Full Text

Department of Internal Medicine Henry Ford Hospital Detroit MI USA.
Division of Cardiology Department of Medicine Henry Ford Hospital Detroit MI USA.
Department of Public Health Sciences Henry Ford Hospital Detroit MI USA.
Division of Gastroenterology and Hepatology Department of Medicine Henry Ford Hospital Detroit MI USA.

Respiratory failure is the most common cause of death in patients with corona virus disease 2019 (COVID-19). There have been many investigations to determine predictors of bad outcomes in patients with this illness. Liver enzyme elevation has been described in hospitalized patients with severe COVID-19; however, little is known about the significance of liver injury regarding outcomes. We conducted a retrospective chart review of 348 patients admitted with COVID-19 in our quaternary care center. Liver injury on admission was defined based on the laboratory cutoff of aspartate aminotransferase >35 IU/L and/or alanine aminotransferase >52 IU/L. Patients were divided into two cohorts based on the presence or absence of liver injury. These cohorts were compared to assess differences in presentation,

complications, and outcomes. The primary outcome was respiratory failure requiring intubation, and the secondary outcome was in-hospital mortality. The presence of new onset liver enzyme elevation on presentation was associated with increased severity of illness, need for mechanical ventilation, and mortality. Presence of liver injury increased the chance of acute hypoxic respiratory failure requiring mechanical ventilation by 1.79 times. The degree and timeline of liver enzyme elevation during hospitalization corresponded with elevations of other inflammatory markers. Conclusion: Liver injury appears to correlate with the inflammatory syndrome caused by COVID-19, with the degree of liver injury corresponding with severity of inflammation. We suggest early and continued monitoring of liver enzymes as they can be useful to identify patients who may need early escalation of care.

Public Health Sciences

Nowak RM, **Jacobsen G**, Limkakeng A, Jr., Peacock WF, Christenson RH, **McCord J**, Apple FS, Singer AJ, and deFilippi CR. Outpatient versus observation/inpatient management of emergency department patients rapidly ruled-out for acute myocardial infarction: Findings from the HIGH-US study. *Am Heart J* 2021; 231:6-17. PMID: 33127532. Full Text

Department of Emergency Medicine, Henry Ford Health System, Detroit, MI.
Department of Epidemiology and Statistics, Henry Ford Health System, Detroit, MI.
Division of Emergency, Medicine, Duke University School of Medicine, Durham, NC.
Department of Emergency Medicine, Baylor College of Medicine, Houston, TX.
University of Maryland School of Medicine, Baltimore, MD.
Heart and Vascular Institute, Henry Ford Health System, Detroit, MI.
Department of Laboratory Medicine and Pathology, Hennepin County Medical Center of Hennepin Healthcare and University of Minnesota Minneapolis, Minneapolis, MN.
Department of Emergency Medicine, SUNY Stony Brook, Stony Brook, New York, NY.
Inova Heart and Vascular Institute, Falls Church, VA. Electronic address: Christopher.Defilippi@Inova.org.

BACKGROUND: The actual Emergency Department (ED) dispositions of patients enrolled in observational studies and meeting criteria for rapid acute myocardial infarction (AMI) rule-out are unknown. Additionally, their presenting clinical profiles, cardiac testing/treatments received, and outcomes have not been reported. METHODS: Patients in the HIGH-US study (29 sites) that ruled-out for AMI using a high-sensitivity cardiac troponin I 0/1-hour algorithm were evaluated. Clinical characteristics of patients having ED discharge were compared to patients placed in observation or hospital admitted (OBS/ADM). Reports of any OBS/ADM cardiac stress test (CST), cardiac catheterization (Cath) and coronary revascularization were reviewed. One year AMI/death and major adverse cardiovascular event rates were determined. RESULTS: Of the 1,020 ruled-out AMI patients 584 (57.3%) had ED discharge. The remaining 436 (42.7%) were placed in OBS/ADM. Patients with risk factors for AMI, including personal or family history of coronary artery disease, hypertension, previous stroke or abnormal ECG were more often placed in OBS/ADM. 175 (40.1%) had a CST. Of these 32 (18.3%) were abnormal and 143 (81.7%) normal. Cath was done in 11 (34.3%) of those with abnormal and 13 (9.1%) with normal CST. Of those without an initial CST 85 (32.6%) had Cath. Overall, revascularizations were performed in 26 (6.0%) patients. One-year AMI/death rates were low/similar (P = .553) for the groups studied. CONCLUSIONS: Rapidly ruled-out for AMI ED patients having a higher clinician perceived risk for new or worsening coronary artery disease and placed in OBS/ADM underwent many diagnostic tests, were infrequently revascularized and had excellent outcomes. Alternate efficient strategies for these patients are needed.

Public Health Sciences

Olufade T, **Lamerato L**, Sánchez JJG, Jiang L, Huang J, Nolan S, and Rangaswami J. Clinical Outcomes and Healthcare Resource Utilization in a Real-World Population Reflecting the DAPA-CKD Trial Participants. *Adv Ther* 2021; Epub ahead of print. PMID: 33474707. Full Text

AstraZeneca, Wilmington, DE, USA. Tope.Olufade@astrazeneca.com.
Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA.
AstraZeneca, Cambridge, UK.

AstraZeneca, Wilmington, DE, USA.
Einstein Medical Center, Philadelphia, PA, USA.

INTRODUCTION: The DAPA-CKD trial assessed dapagliflozin in patients with chronic kidney disease (CKD) with or without type 2 diabetes (T2D). To aid interpretation of results, renal and cardiovascular outcomes plus healthcare resource utilization (HCRU) and costs were assessed in a real-world population similar to that of DAPA-CKD. METHODS: Henry Ford Health System (2006-2016) data were used to identify patients with CKD stages 2-4 [estimated glomerular filtration rate (eGFR) 25-75 ml/min/1.73 m(2) at index and urine albumin-to-creatinine ratio (UACR) 0-5000 mg/g; n = 22,251]. Included patients had confirmatory eGFR ≥ 90 days post-index and no kidney transplant or progression to end-stage kidney disease during 12 months pre-index. The final population (n = 6557) was stratified by UACR (0-29, 30-199 and 200-5000 mg/g; the last comprising the DAPA-CKD-like cohort). Patients were followed for 5 years post-index. RESULTS: Adverse clinical outcomes incidence increased with UACR and was highest for the DAPA-CKD-like cohort (UACR 200-5000 mg/g) versus lower UACR categories (0-29 mg/g and 30-199 mg/g): renal composite outcome (progression to CKD stage 5, dialysis, transplant, ≥ 50% sustained eGFR decline): 26.0% versus 2.2% and 5.8%; heart failure (HF): 36.1% versus 13.9% and 24.6%; myocardial infarction: 11.3% versus 4.7% and 7.4%; stroke: 8.9% versus 4.0% and 5.7%; and mortality: 18.5% versus 6.0% and 11.7%, respectively. Within the DAPA-CKD-like cohort, patients with versus without T2D or HF had a higher frequency of adverse outcomes. The DAPA-CKD-like cohort also had significantly higher annualized per-patient healthcare costs ($39,222/year versus $19,547/year), hospital admission rate (0.55/year versus 0.20/year) and outpatient specialist visit rate (7.55/year versus 6.74/year) versus the lowest UACR category. CONCLUSION: The significant adverse renal and cardiovascular outcomes observed, particularly in the DAPA-CKD-like cohort, represent a substantial burden resulting in increased mortality, HCRU and costs, demonstrating the need for additional treatment options.

Public Health Sciences

Quan D, Luna Wong L, **Shallal A**, Madan R, Hamdan A, Ahdi H, Daneshvar A, Mahajan M, Nasereldin M, **Van Harn M**, Opara IN, and **Zervos M**. Impact of Race and Socioeconomic Status on Outcomes in Patients Hospitalized with COVID-19. *J Gen Intern Med* 2021; Epub ahead of print. PMID: 33506402. Full Text

Wayne State University School of Medicine, Detroit, MI, USA.
Department of Infectious Disease, Henry Ford Hospital, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA.
Department of Internal Medicine, Internal Medicine-Pediatrics Section, Wayne State University School of Medicine, Detroit, MI, USA.
Global Affairs Professor of Medicine, Assistant Dean Wayne State University School of Medicine, MI, Detroit, USA. mzervos1@hfhs.org.
Infectious Diseases, Division Head Henry Ford Health System, MI, Detroit, USA. mzervos1@hfhs.org.

BACKGROUND: The impact of race and socioeconomic status on clinical outcomes has not been quantified in patients hospitalized with coronavirus disease 2019 (COVID-19). OBJECTIVE: To evaluate the association between patient sociodemographics and neighborhood disadvantage with frequencies of death, invasive mechanical ventilation (IMV), and intensive care unit (ICU) admission in patients hospitalized with COVID-19. DESIGN: Retrospective cohort study. SETTING: Four hospitals in an integrated health system serving southeast Michigan. PARTICIPANTS: Adult patients admitted to the hospital with a COVID-19 diagnosis confirmed by polymerase chain reaction. MAIN MEASURES: Patient sociodemographics, comorbidities, and clinical outcomes were collected. Neighborhood socioeconomic variables were obtained at the census tract level from the 2018 American Community Survey. Relationships between neighborhood median income and clinical outcomes were evaluated using multivariate logistic regression models, controlling for patient age, sex, race, Charlson Comorbidity Index, obesity, smoking status, and living environment. KEY RESULTS: Black patients lived in significantly poorer neighborhoods than White patients (median income: $34,758 (24,531-56,095) vs. $63,317 (49,850-85,776), $p < 0.001$) and were more likely to have Medicaid insurance (19.4% vs. 11.2%, $p < 0.001$). Patients from neighborhoods with lower median income were significantly more likely to require

IMV (lowest quartile: 25.4%, highest quartile: 16.0%, p < 0.001) and ICU admission (35.2%, 19.9%, p < 0.001). After adjusting for age, sex, race, and comorbidities, higher neighborhood income ($10,000 increase) remained a significant negative predictor for IMV (OR: 0.95 (95% CI 0.91, 0.99), p = 0.02) and ICU admission (OR: 0.92 (95% CI 0.89, 0.96), p < 0.001). CONCLUSIONS: Neighborhood disadvantage, which is closely associated with race, is a predictor of poor clinical outcomes in COVID-19. Measures of neighborhood disadvantage should be used to inform policies that aim to reduce COVID-19 disparities in the Black community.

Public Health Sciences

Sanders JA, **Vaidyanathan A**, **Sayeed H**, **Sherdiwala B**, **Han X**, **Wyman J**, **Wang DD**, and **O'Neill W**. Comparison of Deep Sedation and General Anesthesia With an Endotracheal Tube for Transcaval Transcatheter Aortic Valve Replacement: A Pioneering Institution's Experience. *J Cardiothorac Vasc Anesth* 2021; Epub ahead of print. PMID: 33441271. Full Text

Department of Anesthesiology, Henry Ford Hospital, Detroit, MI. Electronic address: Jsande11@hfhs.org.
Department of Anesthesiology, Henry Ford Hospital, Detroit, MI.
Department of Statistics, Henry Ford Hospital, Detroit, MI.
Department of Cardiology, Henry Ford Hospital, Detroit, MI.

OBJECTIVES: Transcaval transcatheter aortic valve replacement (TC-TAVR) is an alternative approach to transcatheter aortic valve replacement involving deployment of the bioprosthetic valve via a conduit created from the inferior vena cava to the descending aorta in patients for whom the traditional transfemoral approach is not feasible. By analyzing the largest known cohort of TC-TAVR patients, the authors wished to compare hospital length of stay and post-procedure outcomes between patients who underwent the procedure under deep sedation (DS) and patients who underwent general anesthesia with an endotracheal tube. DESIGN: Retrospective, single-center study. SETTING: Henry Ford Hospital in Detroit, MI. PARTICIPANTS: Patients undergoing TC-TAVR from 2015 to 2018. MEASUREMENTS AND MAIN RESULTS: Seventy-nine patients were included in the analysis, which consisted of 38 under general anesthesia with an endotracheal tube and 41 under DS. The sample was divided into a general anesthesia (GA) group and DS group. There were no significant differences in implant success rate or post-procedure outcomes, including in-hospital mortality (p = 0.999) and major vascular complication rate (p = 0.481), between the two groups. Patients in the GA group stayed a median of 24 hours longer in the intensive care unit (ICU) (p < 0.001) and one day longer in the hospital (p = 0.046) after the procedure compared to patients in the DS group. The median procedure time was significantly lower (135 minutes) in the DS group compared to the GA group (167 minutes, p < 0.001). CONCLUSIONS: Patients undergoing TC-TAVR under DS had similar postoperative outcomes and shorter post-procedure hospital and ICU lengths of stay compared to general anesthesia. In the authors' experience, DS is the preferred anesthetic technique for TC-TAVR.

Public Health Sciences

Tahir RA, **Affan M**, **Marin H**, **Haider SA**, **Alsrouji OK**, **Ahmad A**, **Chebl AB**, **Katramados A**, **Van Harn M**, and **Kole M**. Quantification of pial collateral pressure in acute large vessel occlusion stroke: basic concept with patient outcomes. *Neuroradiology* 2021; Epub ahead of print. PMID: 33507337. Full Text

Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Radiology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Public Health Sciences, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA.
Department of Neurosurgery, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mkole1@hfhs.org.
Department of Radiology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA. mkole1@hfhs.org.

PURPOSE: Pial collateral perfusion to the ischemic penumbra plays a critical role in determining patient outcomes in acute stroke. We aimed to assess the validity and reliability of an intra-procedural technique

for measuring and quantifying the pial collateral pressure (QPCP) to ischemic brain tissue during acute stroke secondary to LVO. QPCP measurements were correlated with standard computed tomography angiography (CTA) and digital subtraction angiography imaging assessments of pial collateral perfusion and outcomes after mechanical endovascular revascularization (MER). METHODS: This prospective cohort study included 60 consecutive patients with middle cerebral artery (MCA)-M1 and proximal M2 occlusions. QPCP measurements were obtained during MER. The validity of QPCP measurements was evaluated using four widely accepted collateral grading scales. QPCP measurements were also analyzed as a predictor of patient outcomes utilizing National Institute of Health Stroke Scale reduction at 24 h and modified Rankin Scale (mRS) scores at 30 days. RESULTS: QPCP measurements and QPCP ratio (QPCP/systemic mean arterial blood pressure) showed a statistically significant association with single-phase pretreatment CTA Maas and American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology binary grading scales. Patient outcomes demonstrated for every 10-unit increase in QPCP, the odds of mRS 0-2 at 30 days increased by 76% ($p = 0.019$). CONCLUSION: QPCP measurements related best with the pretreatment CTA Maas collateral grading scale but were more strongly associated with patient outcomes than any of the four widely accepted collateral grading scales. Greater QPCP was significantly associated with better overall patient outcomes as defined by mRS at 30 days.

Public Health Sciences

Turi KN, McKennan C, Gebretsadik T, Snyder B, Seroogy CM, Lemanske RF, Jr., **Zoratti E**, **Havstad S**, Ober C, Lynch S, McCauley K, Yu C, Jackson DJ, Gern JE, and Hartert TV. Unconjugated bilirubin is associated with protection from early-life wheeze and childhood asthma. *J Allergy Clin Immunol* 2021; Epub ahead of print. PMID: 33434532. Full Text

Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.
Department of Statistics, Pittsburgh University, Pittsburgh, PA, USA.
Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA.
Department of Pediatrics, University of Wisconsin, Madison, WI, USA.
Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA.
Department of Human Genetics, University of Chicago, Chicago, IL, USA.
Division of Gastroenterology, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA.
Department of Pediatrics, University of Wisconsin, Madison, WI, USA. Electronic address: tina.hartert@vumc.org.
Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. Electronic address: gern@medicine.wisc.edu.

BACKGROUND: Wheeze and allergic sensitization are the strongest early-life predictors of childhood asthma development; the molecular origins of these early-life phenotypes are poorly understood. OBJECTIVES: To identify metabolites associated with early-life wheeze, allergic sensitization, and childhood asthma. METHODS: We conducted a nested case-control study using ECHO Program cohorts for discovery and independent replication. Wheeze and allergic sensitization were defined by number of wheeze episodes and positive specific IgE at 1 year of age, respectively. Asthma was defined as physician diagnosis of asthma at age 5 or 6 years. We used untargeted metabolomics, controlling for observed and latent confounding factors, to assess associations between the plasma metabolome and early-life wheeze, allergy, and childhood asthma. RESULTS: Eighteen plasma metabolites were associated with first year wheeze in the discovery cohort (n=338). Z,Z unconjugated bilirubin (UCB) and its related metabolites exhibited a dose-response relationship with wheeze frequency; UCB levels were 13% (β=0.87, 95%CI=0.74-1.02) and 22% (β=0.78, 95%CI=0.68-0.91) lower in children with 1-3 and 4+ wheeze episodes compared to those who never wheezed, respectively. UCB levels were also associated with childhood asthma (β=0.82, 95%CI=0.68-0.98). Similar trends were observed in two independent cohorts. UCB was significantly negatively correlated with eicosanoid- and oxidative stress-related metabolites. There were no significant associations between metabolites and allergic sensitization. CONCLUSIONS: We identified a novel inverse, dose-dependent association between UCB and recurrent wheeze and childhood asthma. Inflammatory lipid mediators and oxidative stress byproducts inversely

correlated with UCB, suggesting UCB modulates pathways critical to the development of early-life recurrent wheeze and childhood asthma.

Public Health Sciences

Varelas PN, **Rehman M**, **Mehta C**, Louchart L, **Schultz L**, **Brady P**, **Kananeh MF**, and Wijdicks EFM. Comparison of 1 vs 2 Brain Death Examinations on Time to Death Pronouncement and Organ Donation: A 12-year Single Center Experience. *Neurology* 2021; Epub ahead of print. PMID: 33514644. Full Text

Department of Neurology, Henry Ford Hospital, Detroit MI, varelap@amc.edu.
Department of Neurology, Henry Ford Hospital, Detroit MI.
Gift of Life of MI, Ann Arbor, MI and Henry Ford Organ Transplant Center, Detroit, MI.
Department of Public Health Sciences, Henry Ford Hospital, Detroit MI.
Division of Neurocritical Care and Hospital Neurology, Mayo Clinic, Rochester, MN.

OBJECTIVE: To fill the evidence gap on the value of a single (SBD) or dual brain death (DBD) exam by providing data on irreversibility of brain function, organ donation consent and transplantation METHODS: 12-year tertiary hospital and organ procurement organization data on brain death (BD) were combined and outcomes, including consent rate for organ donation and organs recovered and transplanted after SBD and DBD were compared after multiple adjustments for co-variatesResults: two-hundred sixty-six patients were declared BD, 122 after SBD and 144 after DBD. Time from event to BD declaration was longer by an average of 20.9 hours after DBD (p=0.003). Seventy-five (73%) families of patients with SBD and 86 (72%) with DBD consented for organ donation (p=0.79). The number of BD exams was not a predictor for consent. No patient regained brain function during the periods following BD. Patients with SBD were more likely to have at least one lung transplanted (p = 0.033). The number of organs transplanted was associated with the number of exams [beta coefficient, (95% CI) -0.5 (-0.97 to -0.02), p=0.044], along with age (for 5 year increase, -0.36 (-0.43 to -0.29), p<0.001) and PaO(2) level (for 10 mmHg increase, 0.026 (0.008 to 0.044), p=0.005) and decreased as the elapsed time to BD declaration increased (p=0.019). CONCLUSIONS: A single neurologic examination to determine brain death is sufficient in patients with non-anoxic catastrophic brain injuries. A second examination is without additional yield in this group and its delay reduces the number of organs transplanted.

Public Health Sciences

Zahoor I, **Rui B**, **Khan J**, **Datta I**, and **Giri S**. An emerging potential of metabolomics in multiple sclerosis: a comprehensive overview. *Cell Mol Life Sci* 2021; Epub ahead of print. PMID: 33449145. Full Text

Department of Neurology, Henry Ford Hospital, Detroit, MI, 48202, USA. izahoor1@hfhs.org.
Department of Neurology, Henry Ford Hospital, Education & Research Building, Room 4023, 2799 W Grand Blvd, Detroit, MI, 48202, USA. izahoor1@hfhs.org.
Department of Neurology, Henry Ford Hospital, Detroit, MI, 48202, USA.
Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, 48202, USA.
Department of Neurology, Henry Ford Hospital, Detroit, MI, 48202, USA. SGiri1@hfhs.org.
Department of Neurology, Henry Ford Hospital, Education & Research Building, Room 4051, 2799 W Grand Blvd, Detroit, MI, 48202, USA. SGiri1@hfhs.org.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the nervous system that primarily affects young adults. Although the exact etiology of the disease remains obscure, it is clear that alterations in the metabolome contribute to this process. As such, defining a reliable and disease-specific metabolome has tremendous potential as a diagnostic and therapeutic strategy for MS. Here, we provide an overview of studies aimed at identifying the role of metabolomics in MS. These offer new insights into disease pathophysiology and the contributions of metabolic pathways to this process, identify unique markers indicative of treatment responses, and demonstrate the therapeutic effects of drug-like metabolites in cellular and animal models of MS. By and large, the commonly perturbed pathways in MS and its preclinical model include lipid metabolism involving alpha-linoleic acid pathway, nucleotide metabolism, amino acid metabolism, tricarboxylic acid cycle, D-ornithine and D-arginine pathways with collective role in signaling and energy supply. The metabolomics studies suggest that metabolic profiling

of MS patient samples may uncover biomarkers that will advance our understanding of disease pathogenesis and progression, reduce delays and mistakes in diagnosis, monitor the course of disease, and detect better drug targets, all of which will improve early therapeutic interventions and improve evaluation of response to these treatments.

Public Health Sciences

Zhang Y, **Han X**, and Shao Y. The ROC of Cox proportional hazards cure models with application in cancer studies. *Lifetime Data Anal* 2021; Epub ahead of print. PMID: 33507457. Full Text

Department of Biostatistics and Research Decision Sciences, Merck & Co., Inc, Kenilworth, NJ, USA.
Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA.
Departments of Population Health & Environmental Medicine, NYU Grossman School of Medicine, 180 Madison Ave, 4th Floor, Suite 455, New York, NY, 10016, USA. Yongzhao.Shao@nyulangone.org.

With recent advancement in cancer screening and treatment, many patients with cancers are identified at early stage and clinically cured. Importantly, uncured patients should be treated timely before the cancer progresses to advanced stages for which therapeutic options are rather limited. It is also crucial to identify uncured subjects among patients with early-stage cancers for clinical trials to develop effective adjuvant therapies. Thus, it is of interest to develop statistical predictive models with as high accuracy as possible in predicting the latent cure status. The receiver operating characteristic curve (ROC) and the area under the ROC curve (AUC) are among the most widely used statistical metrics for assessing predictive accuracy or discriminatory power for a dichotomous outcome (cured/uncured). Yet the conventional AUC cannot be directly used due to incompletely observed cure status. In this article, we proposed new estimates of the ROC curve and its AUC for predicting latent cure status in Cox proportional hazards (PH) cure models and transformation cure models. We developed explicit formulas to estimate sensitivity, specificity, the ROC and its AUC without requiring to know the patient cure status. We also developed EM type estimates to approximate sensitivity, specificity, ROC and AUC conditional on observed data. Numerical studies were used to assess their finite-sample performance of the proposed methods. Both methods are consistent and have similar efficiency as shown in our numerical studies. A melanoma dataset was used to demonstrate the utility of the proposed estimates of the ROC curve for the latent cure status. We also have developed an [Formula: see text] package called [Formula: see text] to efficiently compute the proposed estimates.

Pulmonary and Critical Care Medicine

Awdish R. The Subway. *Chest* 2021; 159(1):435-436. PMID: 33132089. Full Text

Pulmonary and Critical Care Department, Henry Ford Hospital, Detroit, MI. Electronic address: rawdish1@hfhs.org.

Radiation Oncology

Anker CJ, **Dragovic J**, Herman JM, Bianchi NA, Goodman KA, Jones WE, 3rd, Kennedy TJ, Kumar R, Lee P, Russo S, Sharma N, Small W, Suh WW, Tchelebi LT, and Jabbour SK. Executive Summary of the American Radium Society Appropriate Use Criteria for Operable Esophageal and Gastroesophageal Junction Adenocarcinoma: Systematic Review and Guidelines. *Int J Radiat Oncol Biol Phys* 2021; 109(1):186-200. PMID: 32858113. Full Text

Division of Radiation Oncology, University of Vermont Larner College of Medicine, Burlington, Vermont. Electronic address: chris.anker@uvmhealth.org.
Department of Radiation Oncology, Henry Ford Cancer Institute, Henry Ford Hospital, Detroit, Michigan.
Department of Radiation Medicine, Zucker School of Medicine at Hofstra/Northwell, Lake Success, New York.
Department of Reference and Education, Dana Medical Library, University of Vermont, Burlington, Vermont.
Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York City, New York.
Department of Radiation Oncology, UT Health Cancer Center, University of Texas Health Science Center at San Antonio, San Antonio, Texas.

Department of Surgical Oncology, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, New Jersey.
Division of Radiation Oncology, Banner MD Anderson Cancer Center, Gilbert, Arizona.
Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas.
Department of Radiation Oncology, Case Western Reserve University School of Medicine and University Hospitals, Cleveland, Ohio.
Department of Radiation Oncology, Penn State Cancer Institute, Hershey, Pennsylvania.
Department of Radiation Oncology, Loyola University Chicago, Stritch School of Medicine, Cardinal Bernardin Cancer Center, Maywood, Illinois.
Department of Radiation Oncology, University of California at Los Angeles, Ridley-Tree Cancer Center, Santa Barbara, California.
Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, New Jersey.

PURPOSE: Limited guidance exists regarding the relative effectiveness of treatment options for nonmetastatic, operable patients with adenocarcinoma of the esophagus or gastroesophageal junction (GEJ). In this systematic review, the American Radium Society (ARS) gastrointestinal expert panel convened to develop Appropriate Use Criteria (AUC) evaluating how neoadjuvant and/or adjuvant treatment regimens compared with each other, surgery alone, or definitive chemoradiation in terms of response to therapy, quality of life, and oncologic outcomes. METHODS AND MATERIALS: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology was used to develop an extensive analysis of peer-reviewed phase 2R and phase 3 randomized controlled trials as well as meta-analyses found within the Ovid Medline, Cochrane Central, and Embase databases between 2009 to 2019. These studies were used to inform the expert panel, which then rated the appropriateness of various treatments in 4 broadly representative clinical scenarios through a well-established consensus methodology (modified Delphi). RESULTS: For a medically operable nonmetastatic patient with a cT3 and/or cN+ adenocarcinoma of the esophagus or GEJ (Siewert I-II), the panel most strongly recommends neoadjuvant chemoradiation. For a cT2N0M0 patient with high-risk features, the panel recommends neoadjuvant chemoradiation as usually appropriate. For patients found to have pathologically involved nodes (pN+) who did not receive any neoadjuvant therapy, the panel recommends adjuvant chemoradiation as usually appropriate. These guidelines assess the appropriateness of various dose-fractionating schemes and target volumes. CONCLUSIONS: Chemotherapy and/or radiation regimens for esophageal cancer are still evolving with many areas of active investigation. These guidelines are intended for the use of practitioners and patients who desire information about the management of operable esophageal adenocarcinoma.

Radiation Oncology

Ghanem AI, Elsaid AA, **Elshaikh MA**, and Khedr GA. Volumetric-Modulated Arc Radiotherapy with Daily Image-Guidance Carries Better Toxicity Profile for Higher Risk Prostate Cancer. *Asian Pac J Cancer Prev* 2021; 22(1):61-68. PMID: 33507680. Full Text

Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, Michigan, USA.
Department of Clinical Oncology, Faculty of Medicine, Alexandria University, Egypt.

PURPOSE: To compare radiotherapy-induced toxicity for localized prostate-cancer (PCa) treated with versus without daily image-guidance. PATIENTS AND METHODS: We identified consecutive intermediate and high-risk localized PCa patients treated with definitive radiotherapy using intensity-modulated radiotherapy (IMRT) with variable duration of androgen-deprivation therapy (ADT) within 2015-2016 (Arm-A) and 2005-2007 (Arm-B). Arm-A cases received daily online imaging guidance (IGRT) using cone-beam computed tomography (CBCT) unlike Arm-B candidates with no daily IGRT. After reporting demographic, clinico-pathological features and treatment details, we compared acute (within 3 months post-therapy) and late RT-induced toxicities between study groups graded by RTOG/CTCAE criteria. Uni/multivariate analyses (UVA/MVA) were performed to identify independent predictors for RT-related side-effects. RESULTS: We were able to identify 257 cases who met our inclusion criteria. Overall, median age was 73 years (48-85), 67% had intermediate-risk and 47% received ADT. Arm-A included 72 patients who received IMRT delivered using volumetric-modulated arc therapy (VMAT), whereas, Arm-B

was formed of 185 cases who utilized step-and-shoot static IMRT. Clinico-pathological features and treatment details were non-different across study arms except that Arm-A had more Grade Group 3, higher median total dose (79.2 vs. 74 Gy) and more pelvic lymph-nodes RT (p <0.05). Although acute toxicity was similar across groups, Arm-B encountered higher late toxicity score, more intense late genitourinary side-effects (P=0.008), with non-different late lower-gastrointestinal toxicities. On MVA, lack of daily CBCT, African-American race and higher comorbidities were independently predictive for late toxicities. Conclusion: IMRT with daily CBCT permitted safe delivery of dose-escalated IMRT with improved toxicity profile for higher-risk prostate cancer.

Radiation Oncology

Janic B, **Brown SL**, Neff R, Liu F, Mao G, **Chen Y**, **Jackson L**, **Chetty IJ**, **Movsas B**, and **Wen N**. Therapeutic enhancement of radiation and immunomodulation by gold nanoparticles in triple negative breast cancer. *Cancer Biol Ther* 2021; Epub ahead of print. PMID: 33459132. Full Text

Radiation Oncology, Henry Ford Hospital , Detroit, Michigan, USA.
University of Notre Dame , South Bend, Indiana, USA.
Department of Chemical Engineering and Materials Science, Wayne State University , Detroit, Michigan, USA.
School of Chemical Engineering, Unsw Sydney , Kensington, Australia.
Department of Public Health Sciences, Henry Ford Hospital , Detroit, Michigan, USA.

Gold nanoparticles (AuNPs) have been shown to enhance cancer radiotherapy (RT) gain by localizing the absorption of radiation energy in the tumor while sparing surrounding normal tissue from radiation toxicity. Previously, we showed that AuNPs enhanced RT induced DNA damage and cytotoxicity in MCF7 breast cancer cells. Interestingly, we found that cancer cells exhibited a size-dependent AuNPs intracellular localization (4 nm preferentially in the cytoplasm and 14 nm in the nucleus). We extended those studies to an in vivo model and examined the AuNPs effects on RT cytotoxicity, survival and immunomodulation of tumor microenvironment (TME) in human triple negative breast cancer (TNBC) xenograft mouse model. We also explored the significance of nanoparticle size in these AuNPs' effects. Mice treated with RT and RT plus 4 nm or 14 nm AuNPs showed a significant tumor growth delay, compared to untreated animals, while dual RT plus AuNPs treatment exhibited additive effect compared to either RT or AuNPs treatment alone. Survival log-rank test showed significant RT enhancement with 14 nm AuNP alone; however, 4 nm AuNPs did not exhibit RT enhancement. Both sizes of AuNPs enhanced RT induced immunogenic cell death (ICD) that was coupled with significant macrophage infiltration in mice pretreated with 14 nm AuNPs. These results showing significant AuNP size-dependent RT enhancement, as evident by both tumor growth delay and overall survival, reveal additional underlying immunological mechanisms and provide a platform for studying RT multimodal approaches for TNBC that may be combined with immunotherapies, enhancing their effect.

Radiation Oncology

Ramdulari AV, Izzuddeen Y, Benson R, Mallick S, **Venkatesulu B**, and Giridhar P. Laryngeal soft tissue sarcoma: A systematic review and individual patient data analysis of 300 cases. *Head Neck* 2021; Epub ahead of print. PMID: 33448036. Full Text

Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi, India.
Department of Medical Oncology, Regional Cancer Centre, Trivandrum, India.
Department of Radiation Oncology, National Cancer Institute, All India Institute of Medical Sciences, Badsa, India.
Department of Internal Medicine, Henry Ford Hospital, Detroit, USA.

BACKGROUND: Laryngeal sarcoma is rare. We performed a systematic review and individual patient analysis to evaluate the patterns of care, prognostic factors, and role of radiotherapy in laryngeal soft tissue sarcoma. METHODS: A systematic search on PubMed and Google scholar was done. An individual patient data analysis was done. RESULTS: Of the 300 cases of laryngeal sarcoma, 80% underwent surgery. 44% underwent larynx preservation surgery and 25% received radiotherapy with surgery. Median progression free survival (PFS) was 48 months and overall survival (OS) of 224 months

for the entire cohort. Patients with large primary, cartilage invasion, and positive margins had numerically worse PFS. Cartilage invasion and primary tumor size >3 cm were the most common risk factors for adjuvant radiation therapy. Patients receiving radiotherapy were not associated with better survival. CONCLUSION: Laryngeal sarcoma associated with a good survival. Larynx preservation surgery is feasible in nearly half patients. Adjuvant radiotherapy may be warranted in patients poor prognostic factors.

Rheumatology

Sheikh SZ, Scheinberg MA, Wei JCC, Tegzova D, Stohl W, de Toledo RA, Mucenic T, Banfi MRA, **Maksimowicz-McKinnon K**, Abud-Mendoza C, Navarra S, Garcia M, Garcia-De La Torre I, Ros JO, Levy RA, Bass DL, Terrés JR, Punwaney R, Harris J, Nami A, Pierce A, Thorneloe KS, Ji B, and Roth DA. Mortality and adverse events of special interest with intravenous belimumab for adults with active, autoantibody-positive systemic lupus erythematosus (BASE): a multicentre, double-blind, randomised, placebo-controlled, phase 4 trial. *The Lancet Rheumatology* 2021; Epub ahead of print. PMID: Not assigned. Request Article

S.Z. Sheikh, Rheumatology, Allergy & Immunology, University of North Carolina at Chapel Hill, Chapel Hill, United States

Background: Belimumab is approved for the treatment of active systemic lupus erythematosus (SLE). Although clinical trials showed a favourable benefit–risk profile, numerical differences in the incidence of mortality and adverse events of special interest (AESIs) have been reported. We assessed the frequency of these events in patients with SLE receiving belimumab or placebo plus standard therapy. Methods: BASE was a double-blind, randomised, placebo-controlled, phase 4 trial done in 33 countries. Adults with active SLE were randomly assigned (1:1) to receive intravenous belimumab (10 mg/kg) or placebo, plus standard therapy, for 48 weeks. The primary endpoints were incidences of all-cause mortality and AESIs during the on-treatment period (first-to-last study drug dose + 28 days). Safety analyses were done in the as-treated population (patients grouped by actual treatment received >50% of the time). This study was registered with ClinicalTrials.gov (NCT01705977). Findings: Between Nov 27, 2012, and July 28, 2017, we randomly assigned 4018 patients. The as-treated population included 2002 patients in the belimumab group versus 2001 in the placebo group. Ten (0·50%) patients in the belimumab group died versus eight (0·40%) in the placebo group (difference 0·10%, 95% CI −0·31 to 0·51). Incidences were similar in the belimumab and placebo groups for serious infections (75 [3·75%] of 2002 vs 82 [4·10%] of 2001; difference −0·35%, 95% CI −1·55 to 0·85), opportunistic infections and other infections of interest (36 [1·80%] vs 50 [2·50%]; −0·70%, −1·60 to 0·20), non-melanoma skin cancers (4 [0·20%] vs 3 [0·15%]; 0·05%, −0·21 to 0·31) and other malignancies (5 [0·25%] vs 5 [0·25%]; 0·00%, −0·31 to 0·31). A higher proportion of patients in the belimumab group than in the placebo group had infusion and hypersensitivity reactions (8 [0·40%] vs 2 [0·10%]; 0·30%, −0·01 to 0·61), serious depression (7 [0·35%] vs 1 [0·05%]; 0·30%, 0·02 to 0·58), treatment-emergent suicidality (28 [1·42%] of 1972 patients vs 23 [1·16%] of 1986; 0·26%, −0·44 to 0·96), and sponsor-adjudicated serious suicide or self-injury (15 [0·75%] of 1972 patients vs 5 [0·25%] of 1986; post hoc difference 0·50%, 0·06 to 0·94). Interpretation: In line with previously published data, incidences of all-cause mortality and AESIs were similar in patients given belimumab and placebo, except for serious infusion or hypersensitivity reactions, serious depression, treatment-emergent suicidality, and sponsor-adjudicated serious suicide or self-injury events. Funding: GSK.

Surgery

Doshi MD, Tsapepas D, **Prashar R**, Mohan S, Edusei E, Aull MJ, Sherman E, and Dadhania DM. COVID-19 Infection in Former Living Kidney Donors. *Clin Transplant* 2021; Epub ahead of print.:e14230. PMID: 33484065. Full Text

Department of Medicine, Division of Nephrology, University of Michigan, Ann Arbor, MI, USA.
Department of Analytics, New York-Presbyterian Hospital, New York, NY, USA.
Department of Surgery, Division of Transplantation, Columbia University College of Physicians & Surgeons, New York, NY, USA.
Henry Ford Transplant Institute, Detroit, MI, USA.

Department of Medicine, Division of Nephrology, Columbia University College of Physicians & Surgeons, New York, NY, USA.
The Columbia University Renal Epidemiology (CURE) Group, New York, NY, USA.
Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA.
Division of Nephrology and Hypertension, Department of Medicine, Weill Cornell Medicine, New York, NY, USA.
Department of Surgery, Weill Cornell Medicine, New York, NY, USA.
Wayne State University School of Medicine, Detroit, MI, USA.

The COVID-19 pandemic brought living donor kidney transplant programs across the United States to a near halt in March 2020. As programs have begun to reopen, potential donor candidates often inquire about their risk of a COVID-19 infection and its potential impact on kidney function after donation. To address their concerns, we surveyed 1740 former live kidney donors at four transplant centers located in New York and Michigan. Of these, 839 (48.2%) donors responded, their mean age was 46±12.5 years, 543 (65%) were females, and 611 (73%) were white. Ninety-two donors (11%) had symptoms suggestive of a COVID-19 infection with fever (48%) and fatigue (43%) being the most common. Among those with symptoms, 42 donors underwent testing and 16 tested positive. Testing was more common among donors with private insurance and a positive test result was more common among young Black donors. Only one donor surveyed required hospitalization and none required dialysis. Fourteen donors have recovered completely and two partially. Our survey highlights that a COVID-19 infection in former donors results in a mild disease with good recovery. This data will be useful for transplant programs to counsel living donors who are considering kidney donation during this pandemic.

Surgery

Ivanics T, **Williams P**, **Nasser H**, **Leonard-Murali S**, **Schwartz S**, and **Lin JC**. Contemporary management of chronic indwelling inferior vena cava filters. *J Vasc Surg Venous Lymphat Disord* 2021; 9(1):163-169. PMID: 32721588. Full Text

Department of Surgery, Henry Ford Hospital, Detroit, Mich. Electronic address: tivanic1@hfhs.org.
Vascular and Interventional Radiology, Department of Radiology, Henry Ford Hospital, Detroit, Mich.
Department of Surgery, Henry Ford Hospital, Detroit, Mich.
Division of Vascular Surgery, Department of Surgery, Henry Ford Hospital, Detroit, Mich.

OBJECTIVE: Despite increasing retrieval rates of the inferior vena cava (IVC) filter, less than one-third are removed within the recommended timeline. Prolonged filter dwell times may increase the technical difficulty of retrieval and filter-related complications. We sought to evaluate the contemporary outcomes of patients with chronic indwelling IVC filters at a tertiary care center. METHODS: A retrospective analysis was performed from August 2015 through August 2019 of all patients who were referred for removal of a prolonged IVC filter with a dwell time >1 year. Descriptive analysis was used to evaluate patients' characteristics and procedural outcomes, which were reviewed through electronic medical records. Data were expressed as median with interquartile range (IQR) or number and percentage, as appropriate. RESULTS: A total of 47 patients were identified with a median filter dwell time of 10.0 years (IQR, 6-13 years); 34 patients underwent IVC filter removal, and 13 patients refused retrieval. The median age of patients was 54.9 years (IQR, 42.5-64.0 years); the majority were female (57%) and white (53%). The most common indication for filter placement was high risk despite anticoagulation (49%), followed by venous thromboembolism prophylaxis (21%). The majority of patients were symptomatic (72%). If symptomatic, the most common reason for retrieval was IVC penetration (94%), and the chief complaint was pain (56%). Retrieval success was 97%, with a median length of stay of 0 days. The majority of retrievals were performed through an endovascular approach (97%). There was one postprocedural complication (3%). CONCLUSIONS: Despite prolonged dwell times, IVC filter retrieval can be performed safely and effectively in carefully selected patients at a tertiary referral center.

Surgery

Kitajima T, **Henry M**, **Ivanics T**, **Yeddula S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud MS**, **Nagai S**, and **Moonka D**. Incidence and Risk Factors for Fatal Graft-versus-host Disease After Liver Transplantation. *Transplantation* 2021; Epub ahead of print. PMID: 33449608. Full Text

Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI. Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI.

BACKGROUND: Graft-versus-host disease (GVHD) after liver transplantation (LT) is a rare but serious complication. The aim of this study is to identify risk factors, including immunosuppressive regimens, for mortality due to GVHD (fatal GVHD). METHODS: Using data from the OPTN/UNOS registry, 77,416 adult patients who underwent LT between 2003 and 2018 were assessed. Risk factors for fatal GVHD were analyzed by focusing on induction and maintenance immunosuppression regimens. RESULTS: The incidence of fatal GVHD was 0.2% (121/77,416), of whom 105 (87%) died within 180 days and 13 (11%) died between 181 days and 1 year. Median survival after LT was 68.0 (49.5-125.5) days. Recipient age minus donor age greater than 20 years (HR 2.57, P<0.001) and basiliximab induction (HR 1.69, P=0.018) were independent risk factors for fatal GVHD. Maintenance therapy with mycophenolate mofetil (MMF) was associated with a decrease in fatal GVHD (HR 0.51, P=0.001). In an increased risk cohort of patients with recipient-donor age discrepancy greater than 20 years, MMF use was associated with a 50% decline in fatal GVHD (HR 0.50, P<0.001). CONCLUSIONS: Recipient age minus donor age greater than 20 years remains a significant risk factor for fatal GVHD. The risk of fatal GVHD significantly increases in association with basiliximab induction and decreases with MMF maintenance. These associations were pronounced in patients with recipient minus donor age greater than 20 years. These results emphasize the importance of donor age and individualized immunosuppression regimens on the risk of fatal GVHD.

Surgery

Kitajima T, **Moonka D**, **Yeddula S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud MS**, and **Nagai S**. Outcomes in living donor compared to deceased donor primary liver transplant in lower acuity patients with MELD score < 30. *Liver Transpl* 2021; Epub ahead of print. PMID: 33492764. Full Text

Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI, USA.
Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI, USA.

While recent studies have reported favorable outcomes in living donor liver transplantation (LDLT), it remains unclear which populations benefit most from LDLT. The aim of this study is to evaluate post-transplant outcomes in LDLT compared to deceased donor liver transplant (DDLT) according to Model for End-Stage Liver Disease (MELD) score categories. Using data from the OPTN/UNOS registry, outcomes were compared between 1,486 LDLT, 13,568 donation after brain death (DBD) DDLT, and 1,171 donation after circulatory death (DCD) DDLT transplanted between 2009 and 2018. Because LDLT for patients with MELD score >30 was rare (1.8% of all LDLT), all patients with scores > 30 were excluded to equalize LDLT and DDLT cohorts. Risk factors for one-year graft loss were determined in LDLT and DDLT, separately. Compared with LDLT, DBD-DDLT had significantly lower risk of 30-day (aHR 0.60, P<0.001) and one-year graft loss (aHR 0.57, P<0.001). The significantly lower risk of graft loss was more prominent in the mid-MELD score category (score 15-29). DCD-DDLT, compared to LDLT, had significantly lower risk of 30-day graft loss, but comparable risk of one-year graft loss regardless of MELD score category. In LDLT, significant ascites was an independent risk factor for graft loss in patients with mid-MELD scores (aHR 1.68, P=0.02), but not in the lower-MELD score group. Risk of one-year graft loss in LDLT patients with ascites who received left liver was significantly higher than either those who received right liver or those without ascites who received left liver CONCLUSION: In LDLT, combinations of MELD score of 15-29, moderate/severe ascites and use of left liver, are associated with worse outcomes. These findings help calibrate appropriate patient and graft selection in LDLT.

Surgery

Morita Y, Kariya T, **Nagai S**, **Itani A**, **Isley M**, and Tanaka K. Hepatic Vein Flow Index During Orthotopic Liver Transplantation as a Predictive Factor for Postoperative Early Allograft Dysfunction. *J Cardiothorac Vasc Anesth* 2020; Epub ahead of print. PMID: 33455886. Full Text

Department of Anesthesiology, University of Maryland, Baltimore, MD. Electronic address: ymorita@som.umaryland.edu.
Department of Anesthesiology, University of Tokyo, Tokyo, Japan.

Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI.
Department of Anesthesiology, Henry Ford Hospital, Detroit, MI.
Department of Anesthesiology, University of Maryland, Baltimore, MD.

OBJECTIVES: The authors devised a hepatic vein flow index (HVFi), using intraoperative transesophageal echocardiography and graft weight, and investigated its predictive value for postoperative graft function in orthotopic liver transplant. DESIGN: Prospective clinical trial. SETTING, Single-center tertiary academic hospital. PARTICIPANTS: Ninety-seven patients who had orthotopic liver transplant with the piggy-back technique between February 2018 and December 2019. MEASUREMENTS AND MAIN RESULTS: HVFi was defined with HV flow/graft weight. Patients who developed early graft dysfunction (EAD) had low HVFi in systole (HVFi sys, 1.23 v 2.19 L/min/kg, $p < 0.01$), low HVFi in diastole (HVFi dia, 0.87 v 1.54 L/min/kg, $p < 0.01$), low hepatic vein flow (HVF) in systole (HVF sys, 2.04 v 3.95 L/min, $p < 0.01$), and low HVF in diastole (HVF dia, 1.44 v 2.63 L/min, $p < 0.01$). More cardiac death, more vasopressors at the time of measurement, more acute rejection, longer time to normalize total bilirubin (TIME t-bil), longer surgery time, longer neohepatic time, and more packed red blood cell transfusion were observed in the EAD patients. All HVF parameters were negatively correlated with TIME t-bil (HVFi sys $R = -0.406$, $p < 0.01$; HFVi dia $R = -0.442$, $p < 0.01$; HVF sys $R = -0.44$, $p < 0.01$; HVF dia $R = -0.467$, $p < 0.01$). The receiver operating characteristic curve analysis determined the best cut-off levels of HVFi to predict occurrence of EAD (HVFi sys <1.608, HVFi dia <0.784 L/min/kg), acute rejection (HVFi sys <1.388, HVFi dia <1.077 L/min/kg), and prolonged high total bilirubin (HVFi sys <1.471, HVFi dia <1.087 L/min/kg). CONCLUSIONS: The authors' devised HVFi has the potential to predict the postoperative graft function.

Surgery

Mouawad NJ, **Lin JC**, Coleman DM, Simmons J, **Kabbani LS**, Cuff RF, and Mansour MA. The initial experience and response of vascular surgeons in Michigan during the COVID-19 pandemic. *Vascular* 2021; Epub ahead of print. PMID: 33504279. Full Text

Division of Vascular & Endovascular Surgery, McLaren Health System, Bay City, MI, USA.
Division of Vascular Surgery, Henry Ford Health System, Detroit, MI, USA.
Division of Vascular Surgery, University of Michigan, Ann Arbor, MI, USA.
Division of Vascular Surgery, Spectrum Health System, Grand Rapids, MI, USA.

The unprecedented pandemic spread of the novel coronavirus has severely impacted the delivery of healthcare services in the United States and around the world, and has exposed a variety of inefficiencies in healthcare infrastructure. Some states have been disproportionately affected such as New York and Michigan. In fact, Detroit and its surrounding areas have been named as the initial Midwest epicenter where over 106,000 cases have been confirmed in April 2020.Method, Results and Conclusions: Facilities in Southeast Michigan have served as the frontline of the pandemic in the Midwest and in order to cope with the surge, rapid, and in some cases, complete restructuring of care was mandatory to effect change and attempt to deal with the emerging crisis. We describe the initial experience and response of 4 large vascular surgery health systems in Michigan to COVID-19.

Surgery

Nagai S, **Safwan M**, **Kitajima T**, **Yeddula S**, **Abouljoud M**, and **Moonka D**. Disease-Specific Waitlist Outcomes in Liver Transplantation. *Transpl Int* 2021; Epub ahead of print. PMID: 33423330. Full Text

Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI, USA.
Division of Gastroenterology, Henry Ford Hospital, Detroit, MI, USA.

This study aimed to evaluate possible discrepancies in waitlist outcomes between liver diseases, including alcohol-related liver disease (ALD), non-alcoholic steatohepatitis (NASH), hepatitis C virus infection (HCV), primary biliary cirrhosis (PBC), and primacy sclerosing cholangitis (PSC). Patients registered for liver transplantation from January 11, 2016 to June 30, 2018 were evaluated using OPTN/UNOS registry. Waitlist outcomes were compared between the five-disease groups. Patients were categorized by initial MELD-Na-score (6-20, 21-29, and ≥30) to identify outcome variations. Prognostic

impact of transplantation was assessed according to final MELD-Na scores using Cox-regression analysis modeling transplantation as a time-dependent covariate. 6,053 with ALD, 3,814 with NASH, 1,558 with HCV, 602 with PBC, and 819 with PSC were eligible. Compared to ALD with comparable MELD-Na-scores, NASH with lower (adjusted hazard ratio [aHR]=1.30, P=0.042) and mid-scores (aHR=1.35, P=0.008) showed significantly higher risk of 1-year waitlist mortality, and PBC with higher scores showed significantly higher risk of 90-day (aHR=1.69, P=0.03) and 1-year waitlist mortality (aHR=1.69, P=0.02). Positive prognostic impact of transplantation was not seen until score of 24-27 in ALD, 18-20 in HCV, 15-17 in NASH, and 24-27 in PBC and PSC. There are significant differences in waitlist outcomes among etiologies, which may differ the optimal transplant timing.

Surgery

Shamaa O, **Jafri SM**, **Shamaa MT**, **Brown K**, and **Venkat D**. Takotsubo Cardiomyopathy Following Liver Transplantation: A Report of 2 Cases. *Transplant Proc* 2021; 53(1):239-243. PMID: 32980136. Full Text

Internal Medicine, Henry Ford Hospital, Detroit, Michigan, United States. Electronic address: Omaar10y@gmail.com.
Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan, United States.
General Surgery, Henry Ford Hospital, Detroit, Michigan, United States.

PURPOSE: Takotsubo cardiomyopathy, also called apical ballooning syndrome, is characterized by regional left ventricular systolic dysfunction that resembles myocardial infarction in its initial presentation; however, it lacks angiographic evidence of coronary artery disease. We evaluated the incidence of takotsubo cardiomyopathy following liver transplant at a diverse urban transplant program. METHODS: This is a retrospective review of patients transplanted at a single center between 2017 and 2019. Here we report 2 cases of takotsubo cardiomyopathy that developed after liver transplantation. RESULTS: A 65-year-old woman diagnosed with alcoholic cirrhosis underwent a brain-dead donor liver transplant. The postoperative course was complicated by stroke, pulmonary hypertension, and a left internal jugular thrombus. Six months following transplant, the patient developed takotsubo cardiomyopathy with congestive hepatopathy and died of heart failure complications despite maximal medical care. The second case was a 65-year-old woman with alcoholic cirrhosis admitted for a living donor liver transplant. The postoperative period involved recurrent seizures and elevated troponins with markedly reduced ejection fraction, which were appropriately managed. The patient recovered well with supportive care and was discharged to a rehabilitation facility shortly after. CONCLUSION: We present a series of patients with takotsubo cardiomyopathy after liver transplantation. The diagnosis depends on the clinical presentation and findings on electrocardiography, echocardiography, and cardiac enzymes. Our patients met the Mayo Clinic diagnostic criteria and were appropriately managed according to guidelines. Our report highlights the possibility of pulmonary hypertension contributing to the development of takotsubo cardiomyopathy. Additional studies are needed to establish a definite correlation.

Surgery

Turcotte J, Callanan M, **Buckley B**, Zaidi S, and Patton C. Conversion of PROMIS global health to EQ-5D health state values in patients undergoing lumbar spine surgery: A psychometric evaluation. *J Orthop* 2021; 23:67-72. PMID: 33456218. Full Text

Anne Arundel Medical Center, Annapolis, MD, USA.
Medical University of South Carolina, Charleston, SC, USA.
Henry Ford Wyandotte Hospital, Wyandotte, MI, USA.

This study seeks to validate the conversion of PROMIS-GH scores to EQ-5D Health Utility Index (HUI) values. Patients undergoing lumbar spine surgery were prospectively surveyed using EQ-5D-3L and PROMIS-GH short form instruments. EQ-5D-HUI scores, and PROMIS scores converted to HUI were calculated. Neither instrument demonstrated any floor effects. The EQ-5D-HUI demonstrated significantly higher ceiling effects. Patients reported a significantly higher mean HUI score using the EQ-5D compared to PROMIS-GH. Strong positive correlation and agreement were observed. Conversion of the PROMIS-GH to the EQ-5D-HUI appears to be viable for evaluating the health status of patients undergoing lumbar spine surgery.

Undergraduate Medical Education

Kitajima T, **Henry M**, **Ivanics T**, **Yeddula S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud MS**, **Nagai S**, and **Moonka D**. Incidence and Risk Factors for Fatal Graft-versus-host Disease After Liver Transplantation. *Transplantation* 2021; Epub ahead of print. PMID: 33449608. Full Text

Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI. Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI.

BACKGROUND: Graft-versus-host disease (GVHD) after liver transplantation (LT) is a rare but serious complication. The aim of this study is to identify risk factors, including immunosuppressive regimens, for mortality due to GVHD (fatal GVHD). METHODS: Using data from the OPTN/UNOS registry, 77,416 adult patients who underwent LT between 2003 and 2018 were assessed. Risk factors for fatal GVHD were analyzed by focusing on induction and maintenance immunosuppression regimens. RESULTS: The incidence of fatal GVHD was 0.2% (121/77,416), of whom 105 (87%) died within 180 days and 13 (11%) died between 181 days and 1 year. Median survival after LT was 68.0 (49.5-125.5) days. Recipient age minus donor age greater than 20 years (HR 2.57, P<0.001) and basiliximab induction (HR 1.69, P=0.018) were independent risk factors for fatal GVHD. Maintenance therapy with mycophenolate mofetil (MMF) was associated with a decrease in fatal GVHD (HR 0.51, P=0.001). In an increased risk cohort of patients with recipient-donor age discrepancy greater than 20 years, MMF use was associated with a 50% decline in fatal GVHD (HR 0.50, P<0.001). CONCLUSIONS: Recipient age minus donor age greater than 20 years remains a significant risk factor for fatal GVHD. The risk of fatal GVHD significantly increases in association with basiliximab induction and decreases with MMF maintenance. These associations were pronounced in patients with recipient minus donor age greater than 20 years. These results emphasize the importance of donor age and individualized immunosuppression regimens on the risk of fatal GVHD.

Undergraduate Medical Education

Olds H, **Liu J**, **Luk K**, **Lim HW**, **Ozog D**, and **Rambhatla PV**. Telogen effluvium associated with COVID-19 infection. *Dermatol Ther* 2021; Epub ahead of print. PMID: 33405302. Full Text

Wayne State University School of Medicine, Detroit, Michigan, USA.
Department of Dermatology, Henry Ford Hospital, Detroit, Michigan, USA.

Telogen effluvium (TE) is characterized by diffuse hair shedding 2-3 months after a stressor, and COVID-19 infection is potentially one such stressor. Those who were infected with the virus were under immense psychosocial and physiologic stress. We retrospectively reviewed electronic medical records of 552 patients who were evaluated by a Henry Ford Health System dermatologist between February 2020 and September 2020 and had a diagnosis of COVID-19 infection. Ten patients were identified with TE attributed to COVID-19 infection and described their presentations as a case series. For the ten patients selected, the mean age was 48.5 years old and 90% were female. Six of the patients were Black, one Middle Eastern, and three White. On average, the hair shedding began 50 days after the first symptom of COVID-19 infection. About 80% of these patients were treated with antibiotics, systemic corticosteroids, and/or hydroxychloroquine for their COVID-19 infection and 70% were hospitalized. The presentations of these patients suggest that COVID-19 infection may be a significant trigger of TE. TE caused by hydroxychloroquine, azithromycin or other medications cannot be ruled out, and the global pandemic itself is a source of psychosocial stress. Further studies will be needed to understand the long-term prevalence and prognosis of TE associated with COVID-19 infection.

Urology

Abou-Ouf H, Assem H, Ghosh S, Karnes RJ, Stoletov K, **Palanisamy N**, Lewis JD, and Bismar TA. High Serine-arginine Protein Kinase 1 Expression with PTEN Loss Defines Aggressive Phenotype of Prostate Cancer Associated with Lethal Outcome and Decreased Overall Survival. *European Urology Open Science* 2021; 23:1-8. PMID: Not assigned. Full Text

T.A. Bismar, Departments of Pathology and Laboratory Medicine and Oncology University of Calgary, Cumming School of Medicine Rockyview General Hospital Calgary, Canada

Background: Serine-arginine protein kinase 1 (SRPK1) has been implicated in prostate cancer (PCa) progression. However, its prognostic value and association with ERG and PTEN expression, two of the most common genetic alterations, have not been explored fully. Objective: We assessed the prognostic value of SRPK1 in association with ERG and PTEN in a cohort of patients managed nonsurgically by androgen deprivation therapy (ADT) for advanced disease. Design, setting, and participants: The study cohort consisted of men diagnosed with PCa by transurethral resection of the prostate (TURP; n = 480). The patients were divided into three main groups: incidental (patients with Gleason score [GS] ≤7 with no prior ADT), advanced (patients with GS ≥8 with no prior ADT), and castrate-resistant PCa (patients with prior ADT). Outcome measurements and statistical analysis: A total of 480 TURP samples were assessed by immunohistochemistry for SRPK1, ERG, and PTEN, and results were correlated with Gleason grade group (GG), overall survival (OS), and PCa-specific mortality (PCSM). Results and limitations: High SRPK1 expression was noted in 105/455 (23%) available patient cores. Expression of SRPK1 was associated with Gleason grade grouping ($p < 0.0001$) with high expression detected in 22/74 (33%) with GG 5. High SRPK1 was not associated with ERG positivity ($p = 0.18$) but was significantly associated with PTEN intensity ($p = 0.001$). High SRPK1 was associated with OS (hazard ratio [HR] 1.99; confidence interval [CI]: 1.57–2.54, $p < 0.0001$) and PCSM (HR 1.64; CI: 1.19–2.26, $p < 0.002$). Adjusting for Gleason score, patients with high SRPK1 and negative PTEN had the worst clinical outcome for both OS and PCSM compared with other patients ($p < 0.0001$, HR: 3.02; CI: 1.87–4.88 and HR: 6.40, CI: 3.19–12.85, respectively). Conclusions: High SRPK1 is associated with worse OS and PCSM. Moreover, patients with high SRPK1 expression and loss of PTEN had the worst clinical outcome for OS and cancer-specific mortality. Combined status of SRPK1 and PTEN may provide added value in stratifying patients into various prognostic groups. Patient summary: The expression of serine-arginine protein kinase 1 (SRPK1) combined with PTEN has a significant prognostic role in prostate cancer patients. Patients with high SRPK1 expression and negative PTEN had the worst clinical outcome for overall survival and cancer-specific mortality.

Urology

Auffenberg GB, Qi J, Dunn RL, Linsell S, Kim T, Miller DC, Tosoian J, Sarle R, Johnston WK, 3rd, Kleer E, Ghani KR, Montie J, and **Peabody J**. Evaluation of Patient- and Surgeon-Specific Variations in Patient-Reported Urinary Outcomes 3 Months After Radical Prostatectomy From a Statewide Improvement Collaborative. *JAMA Surg* 2021; Epub ahead of print. PMID: 33471043. Full Text

Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.
Department of Urology, University of Michigan, Ann Arbor.
Department of Orthopedic Surgery, University of Michigan, Ann Arbor.
Department of Urology, Sparrow Hospital, Lansing, Michigan.
Michigan Institute of Urology, Novi.
IHA Urology, St Joe's Ann Arbor, Ann Arbor, Michigan.
Department of Urology, Henry Ford Health System, Detroit, Michigan.

IMPORTANCE: Understanding variation in patient-reported outcomes following radical prostatectomy may inform efforts to reduce morbidity after this procedure. OBJECTIVE: To describe patient-reported urinary outcomes following radical prostatectomy in the diverse practice settings of a statewide quality improvement program and to explore whether surgeon-specific variations in observed outcomes persist after accounting for patient-level factors. DESIGN, SETTING, AND PARTICIPANTS: This prospective population-based cohort study included 4582 men in the Michigan Urological Surgery Improvement Collaborative who underwent radical prostatectomy as primary management of localized prostate cancer between April 2014 and July 2018 and who agreed to complete validated questionnaires prior to surgery and at 3, 6, and 12 months after surgery. Data were analyzed from 2019 to June 2019. EXPOSURES: Radical prostatectomy. MAIN OUTCOMES AND MEASURES: Patient- and surgeon-level analyses of patient-reported urinary function 3 months after radical prostatectomy. Outcomes were measured using validated questionnaires with results standardized using previously published methods. Urinary function survey scores are reported on a scale from 0 to 100 with good function established as a score of 74 or higher. RESULTS: For the 4582 men undergoing radical prostatectomy within the Michigan Urological Surgery Improvement Collaborative who agreed to complete surveys, mean (SD) age was 63.3 (7.1)

years. Survey response rates varied: 3791 of 4582 (83%) responded at baseline, 3282 of 4137 (79%) at 3 months, 2975 of 3770 (79%) at 6 months, and 2213 of 2882 (77%) at 12 months. Mean (SD) urinary function scores were 88.5 (14.3) at baseline, 53.6 (27.5) at 3 months, 68.0 (25.1) at 6 months, and 73.7 (23.0) at 12 months. Regression analysis demonstrated that older age, lower baseline urinary function score, body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or higher, clinical stage T2 or higher, and lack of bilateral nerve-sparing surgery were associated with a lower probability of reporting good urinary function 3 months after surgery. When evaluating patients with good baseline function, the rate at which individual surgeons' patients reported good urinary function 3 months after surgery varied broadly (0% to 54.5%; P < .001). Patients receiving surgery from top-performing surgeons were more likely to report good 3-month function. This finding persisted after accounting for patient risk factors. CONCLUSIONS AND RELEVANCE: In this study, patient- and surgeon-level urinary outcomes following prostatectomy varied substantially. Documenting surgeon-specific variations after accounting for patient factors may facilitate identification of surgical factors associated with superior outcomes.

Urology

Dalela D, **Palma-Zamora I**, and **Rogers C**. Re: Fredrick Leidberg, Petter Kollberg, Marie Allerbo, et al. Preventing Parastomal Hernia After Ileal Conduit by the Use of a Prophylactic Mesh: A Randomised Study. Eur Urol 2020;78:757-63. *Eur Urol* 2021; Epub ahead of print. PMID: 33487478. Full Text

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA. Electronic address: ddalela1@hfhs.org.
Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA.

Urology

Johnson K, Lane BR, Weizer AZ, Herrel LA, **Rogers CG**, Qi J, Johnson AM, Seifman BD, and Sarle RC. Partial nephrectomy should be classified as an inpatient procedure: Results from a statewide quality improvement collaborative. *Urol Oncol* 2021; Epub ahead of print. PMID: 33485765. Full Text

Michigan Medicine, Ann Arbor, MI.
Michigan State University College of Human Medicine, Grand Rapids, MI; Spectrum Health Hospital System, Grand Rapids, MI. Electronic address: brian.lane@spectrumhealth.org.
Henry Ford Health System, Detroit, MI.
Michigan Institute of Urology, Troy, MI.
Sparrow Medical Group, Lansing, MI.

OBJECTIVES: To examine length of stay (LOS) and readmission rates for all minimally-invasive partial nephrectomy (MIPN) and MI radical nephrectomy (MIRN) performed for localized renal masses ≤7 cm in size (cT1RM) within 12 Michigan urology practices. Both RN and PN are commonly performed in treating cT1RM. Although technically more complex and associated with higher complication rates, Centers for Medicare & Medicaid Services considers MIPN an outpatient procedure and MIRN is inpatient. METHODS: We collected data for renal surgeries for cT1RM at MUSIC-KIDNEY practices between May 2017-February 2020. Data abstractors recorded clinical, radiographic, pathologic, surgical, and short-term follow-up data into the registry for cT1RM patients. RESULTS: Within MUSIC-KIDNEY, 807 patients underwent MI renal surgery at 12 practices. Median LOS for cT1RM patients after MIPN (n = 531, 66%) was 2 days and after MIRN (n = 276, 34%) was also 2 days. Among patients undergoing laparoscopic or robotic PN, 171 (32%), 230 (43%), and 130 (24%) stayed ≤1, 2, ≥3 days. Among patients undergoing laparoscopic or robotic RN, 81 (29%), 112 (41%), and 83 (30%) stayed ≤1, 2, ≥3 days. No significant difference was observed between MIPN and MIRN on LOS commensurate with outpatient surgery (≤1-day, OR = 0.97, P = 0.87). CONCLUSIONS: Less than one-third of patients had a LOS ≤1-day and LOS was comparable for MIPN and MIRN. Centers for Medicare & Medicaid Services should be advised that MIPN is a more complex surgery than MIRN, most patients receiving a MIPN will require a ≥2-day hospital stay and it would be more appropriate to classify MIPN an inpatient procedure with MIRN.

Urology

Lee DI, **Shahait M**, Dalela D, Keeley J, Lal P, Vapiwala N, and **Abdollah F**. External validation of genomic classifier-based risk-stratification tool to identify candidates for adjuvant radiation therapy in patients with prostate cancer. *World J Urol* 2021; Epub ahead of print. PMID: 33388922. Full Text

Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA.
Department of Surgery, King Hussein Cancer Center, Amman, Jordan.
Vattikuti Urology Institute (VUI), Henry Ford Hospital, Detroit, USA.
Department of Pathology, Perelman School of Medicine University of Pennsylvania, Philadelphia, USA.
Department of Radiation Oncology, Perelman School of Medicine University of Pennsylvania, Philadelphia, USA.
Wayne State University, Detroit, USA.
VUI Center for Outcomes Research Analytics and Evaluation, Senior staff, Vattikuti Urology Institute (VUI), Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202-2689, USA.
firas.abdollah@gmail.com.

OBJECTIVE: To externally validate a Genomic Classifier (GC) based risk-stratification nomogram identifying candidates who would benefit from adjuvant radiation (aRT) therapy after radical prostatectomy (RP). METHODS: We identified 350 patients who underwent RP, between 2013 and 2018, and had adverse pathological features (positive margin, and/or pT3a or higher) on final pathology. Genomic profile was available for all these men. The clinical recurrence-free survival was estimated using the Kaplan-Meier method. The external validity of the nomogram was tested using the concordance index (c-index), calibration plot, and decision curve analysis. RESULTS: The median follow-up of the cohort was 26.5 months. Overall, 14% of the patients received aRT. During the follow-up period, 3.4% of the patients developed metastasis. Overall 3-year metastasis-free survival was 95% (95% CI 0.92-0.98). The c-index of the nomogram was 0.84. The calibration of the model was favorable. Decision-curve analysis showed a positive net benefit for probabilities ranging between 0.01 and 0.09, with the highest difference at threshold probability around 0.05. At that threshold, the net benefit is 0.06 for the model and 0 for treating all the patients. CONCLUSION: Our report is the first to confirm the validity of this genomic-based risk-stratification tool in identifying men who might benefit from aRT after RP. As such, it can be a useful instrument to be incorporated in shared decision making on whether administration of aRT will lead to a clinically meaningful benefit. Such a model can also be useful for patients' classification in future clinical trials.

Urology

Patel AK, **Rogers CG**, Johnson A, Noyes SL, Qi J, Miller D, Shervish E, Stockton B, and Lane BR. Initial Observation of a Large Proportion of Patients Presenting with Clinical Stage T1 Renal Masses: Results from the MUSIC-KIDNEY Statewide Collaborative. *European Urology Open Science* 2021; 23:13-19. PMID: Not assigned. Full Text

B.R. Lane, Betz Family Chair for Cancer Research, Spectrum Health Cancer Center, Urology Division, Spectrum Health Medical Group, 145 Michigan Street NE, Suite 5500, Grand Rapids, MI, United States

The Michigan Urological Surgery Improvement Collaborative—Kidney mass: Identifying and Defining Necessary Evaluation and therapY (MUSIC-KIDNEY) quality improvement collaborative has shown that initial observation of a renal mass <7 cm in size is used in almost half of patients. Age, tumor size, and cystic lesions appear to be associated with its utilization.

Urology

Rambhatla A, Bronkema CJ, Corsi N, Keeley J, **Sood A**, Affas Z, **Dabaja AA**, **Rogers CG**, **Liroff SA**, and **Abdollah F**. COVID-19 Infection in Men on Testosterone Replacement Therapy. *J Sex Med* 2021; 18(1):215-218. PMID: 33191186. Full Text

Department of Urology, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA. Electronic address: Arambha1@hfhs.org.

School of Medicine, Wayne State University, Detroit, MI, USA; Center for Outcomes Research Analytics and Evaluation, Vattikuti Urology Institute, Detroit, MI, USA.
Center for Outcomes Research Analytics and Evaluation, Vattikuti Urology Institute, Detroit, MI, USA.
Department of Urology, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA; Center for Outcomes Research Analytics and Evaluation, Vattikuti Urology Institute, Detroit, MI, USA.
Department of Urology, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA.

BACKGROUND: Men who contract coronavirus disease 2019 (COVID-19) appear to have worse clinical outcomes compared with women which raises the possibility of androgen-dependent effects. AIM: We sought to determine if testosterone replacement therapy (TRT) is associated with worse clinical outcomes. METHODS: Through a retrospective chart review, we identified 32 men diagnosed with COVID-19 and on TRT. They were propensity score matched to 63 men diagnosed with COVID-19 and not on TRT. Data regarding comorbidities and endpoints such as hospital admission, intensive care unit admission, ventilator utilization, thromboembolic events, and death were extracted. Chi-square and Kruskal-Wallis tests examined differences in categorical and continuous variables, respectively. Logistic regression analysis tested the relationship between TRT status and the study endpoints. RESULTS: There were no statistically significant differences between the 2 groups, and TRT was not a predictor of any of the endpoints on multivariate analysis. CONCLUSION: These results suggest that TRT is not associated with a worse clinical outcome in men diagnosed with COVID-19. Rambhatla A, Bronkema CJ, Corsi N, et al. COVID-19 Infection in Men on Testosterone Replacement Therapy. J Sex Med 2021;18:215-218.

Conference Abstracts

Endocrinology and Metabolism

Minisola S, Colangelo L, Pepe J, Diacinti D, Cipriani C, and **Rao SD**. Osteomalacia and Vitamin D Status: A Clinical Update 2020. *JBMR Plus* 2021; 5(1).

S. Minisola, Department of Clinical, Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

Historically, rickets and osteomalacia have been synonymous with vitamin D deficiency dating back to the 17th century. The term osteomalacia, which literally means soft bone, was traditionally applied to characteristic radiologically or histologically documented skeletal disease and not just to clinical or biochemical abnormalities. Osteomalacia results from impaired mineralization of bone that can manifest in several types, which differ from one another by the relationships of osteoid (ie, unmineralized bone matrix) thickness both with osteoid surface and mineral apposition rate. Osteomalacia related to vitamin D deficiency evolves in three stages. The initial stage is characterized by normal serum levels of calcium and phosphate and elevated alkaline phosphatase, PTH, and 1,25-dihydroxyvitamin D [1,25(OH)2D]—the latter a consequence of increased PTH. In the second stage, serum calcium and often phosphate levels usually decline, and both serum PTH and alkaline phosphatase values increase further. However, serum 1,25(OH)2D returns to normal or low values depending on the concentration of its substrate, 25-hydroxyvitamin D (25OHD; the best available index of vitamin D nutrition) and the degree of PTH elevation. In the final stage, hypocalcemia and hypophosphatemia are invariably low with further exacerbation of secondary hyperparathyroidism. The exact,or even an approximate, prevalence of osteomalacia caused by vitamin D deficiency is difficult to estimate, most likely it is underrecognized or misdiagnosed as osteoporosis. Signs and symptoms include diffuse bone, muscle weakness, and characteristic fracture pattern, often referred to as pseudofractures, involving ribs, scapulae, pubic rami, proximal femurs, and codfish-type vertebrae. The goal of therapy of vitamin D-deficiency osteomalacia is to alleviate symptoms, promote fracture healing, restore bone strength, and improve quality of life while correcting biochemical abnormalities. There is a need for better understanding of the epidemiology of osteomalacia. Simplified tools validated by concurrent bone histology should be developed to help clinicians promptly diagnose osteomalacia.

Hematology-Oncology

Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, Doebele RC, Cassier P, Lopes G, Tan DSW, Garralda E, Paz-Ares L, Cho BC, **Gadgeel SM**, Thomas M, Liu SV, Clifford C, Zhang H, Turner CD, and Subbiah V. MO01.38 Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced RET Fusion+ Non-Small-Cell Lung Cancer (NSCLC). *Journal of Thoracic Oncology* 2021; 16(1):S31-S32.

Background: Pralsetinib is an investigational, highly potent, selective RET inhibitor. We provide the registrational dataset for patients with RET fusion+ NSCLC with and without prior treatment from ARROW. Methods: ARROW (75 sites/11 countries; NCT03037385) consists of phase 1 dose escalation to establish recommended phase 2 dose (400 mg once daily [QD] orally) and phase 2 expansion cohorts defined by tumor type and/or RET alteration. Primary objectives were overall response rate (ORR; blinded independent central review per RECIST v1.1) and safety. Efficacy is shown for response-evaluable patients (REP) with RET fusion+ NSCLC who initiated 400 mg QD pralsetinib by July 11, 2019 and safety for all patients (all diagnoses) who initiated 400 mg QD. Results: As of November 18, 2019, 354 patients with advanced solid tumors had initiated 400 mg QD pralsetinib (median follow-up 8.8 months). Efficacy outcomes are shown (Table) for patients with metastatic RET fusion+ NSCLC (n=116; 72% KIF5B; 16% CCDC6; 12% other/fusion present but type unknown) with prior platinum treatment (n=80) or without prior systemic treatment (n=26). ORR was similar regardless of RET fusion partner, prior therapies, or central nervous system involvement. Overall there were 7 (6%) complete responses, 4 (5%) in prior platinum patients and 3 (12%) in treatment-naïve patients; median time to response overall was 1.8 months and median duration of response (DOR) was not reached (95% CI, 11.3–not reached). In the safety population (n=354; all tumor types), most treatment-related adverse events (TRAEs) were grade 1–2, and included increased aspartate aminotransferase (31%), anemia (22%), increased alanine aminotransferase (21%), constipation (21%) and hypertension (20%). 4% of patients in the safety population discontinued due to TRAEs. Conclusions: Pralsetinib has rapid, potent, and durable clinical activity in patients with advanced RET fusion+ NSCLC regardless of RET fusion genotype or prior therapies, and QD oral dosing is well-tolerated. [Formula presented]

Hematology-Oncology

Spigel D, Waqar SN, Burkard ME, Lin JJ, Chae YK, Socinski MA, **Gadgeel S**, Reckamp KL, Leland SM, Plessinger D, Kunkel L, Bauman JR, Otterson G, Halmos B, Ignatius Ou SH, Patil T, Elamin YY, and Kim ES. MO01.33 CRESTONE – Clinical Study of REsponse to Seribantumab in Tumors with NEuregulin-1 (NRG1) Fusions – A Phase 2 Study of the anti-HER3 mAb for Advanced or Metastatic Solid Tumors (NCT04383210). *Journal of Thoracic Oncology* 2021; 16(1):S29-S30.

Background: NRG1 (Neuregulin-1) gene fusions are rare oncogenic drivers found in 0.2% of solid tumors, including lung, pancreatic, gallbladder, breast, ovarian, colorectal, neuroendocrine, and sarcomas. NRG1 is the predominant ligand of HER3 and to a lesser extent HER4. NRG1 fusion proteins retaining an active EGF-like domain drive tumorigenesis and proliferation through aberrant HER3 activation. Importantly, NRG1 fusions are often mutually exclusive with other known driver alterations. NRG1 fusions have been correlated with worse overall and disease-free survival and poor response to treatment with standard therapies including chemotherapy, PD-(L)1 checkpoint inhibitors and combinations of these agents. Inhibition of HER3 and its dimerization partners represents a rational and novel therapeutic approach for tumors harboring an NRG1 fusion supported by case studies of clinical responses to anti-HER3 antibodies or pan-ERBB (tyrosine kinase inhibitors) TKIs like afatinib. Seribantumab is a fully human IgG2 mAb against HER3 uniquely able to inhibit NRG1-dependent activation of HER3, HER3-HER2 dimerization, and downstream signaling through the PI3K/AKT and MAPK pathways. The clinical safety profile of seribantumab has been well characterized through prior monotherapy and combination studies in over 800 patients. Methods: CRESTONE is an open label, multicenter Phase 2 basket trial of seribantumab in adult patients with NRG1 fusion-positive locally advanced or metastatic solid tumors who have progressed on or are nonresponsive to available therapies. The trial will enroll at least 75 previously treated patients across three cohorts. Cohort 1 (N=55) will include patients who have not received prior treatment with any ERBB targeted therapy. Cohort 2 (up to N=10) will include patients who have progressed after prior treatment which includes ERBB targeted therapy. Cohort 3 (up to N=10) will include

patients harboring NRG1 fusions without an EGF-like binding domain. NRG1 fusion status for enrollment will be determined through a local CLIA or similarly accredited molecular assay. NRG1 fusion status for patients in Cohort 1 will be centrally confirmed using an RNA-based NGS assay. This study will evaluate a novel dosing regimen of weekly induction, biweekly consolidation, and Q3W maintenance designed to rapidly achieve steady state levels, optimize exposure, and deliver maximal NRG1 inhibition. The primary endpoint is ORR per RECIST v1.1 by independent radiologic review. Secondary endpoints include duration of response (DoR), safety, PFS, OS, and overall clinical benefit rate. An interim analysis is planned following enrollment of 20 patients in Cohort 1. CRESTONE is open and accruing patients in the United States. Clinical trial information: NCT04383210.

HFHS Publications on COVID-19

Administration
Brawner CA, **Ehrman JK**, **Bole S**, **Kerrigan DJ**, **Parikh SS**, **Lewis BK**, **Gindi RM**, **Keteyian C**, **Abdul-Nour K**, and **Keteyian SJ**. Inverse Relationship of Maximal Exercise Capacity to Hospitalization Secondary to Coronavirus Disease 2019. *Mayo Clin Proc* 2021; 96(1):32-39. PMID: 33413833. Full Text

Cardiology/Cardiovascular Research
Brawner CA, **Ehrman JK**, **Bole S**, **Kerrigan DJ**, **Parikh SS**, **Lewis BK**, **Gindi RM**, **Keteyian C**, **Abdul-Nour K**, and **Keteyian SJ**. Inverse Relationship of Maximal Exercise Capacity to Hospitalization Secondary to Coronavirus Disease 2019. *Mayo Clin Proc* 2021; 96(1):32-39. PMID: 33413833. Full Text

Cardiology/Cardiovascular Research
Mishra K, **Naffouj S**, **Gorgis S**, **Ibrahim H**, **Gill S**, **Fadel R**, **Chatfield A**, **Tang A**, and **Salgia R**. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. *Hepatol Commun* 2021; 5(1):24-32. PMID: 33437898. Full Text

Cardiology/Cardiovascular Research
Raad M, **Gorgis S**, **Dabbagh M**, Chehab O, **Parikh S**, and **Singh G**. Right Heart Strain on Presenting 12-Lead Electrocardiogram Predicts Critical Illness in COVID-19. *JACC Clin Electrophysiol* 2020; Epub ahead of print. PMID: 33358667. Full Text

Dermatology
McMahon DE, Gallman AE, Hruza GJ, Rosenbach M, Lipoff JB, Desai SR, French LE, **Lim H**, Cyster JG, Fox LP, Fassett MS, and Freeman EE. Long COVID in the skin: a registry analysis of COVID-19 dermatological duration. *Lancet Infect Dis* 2021; Epub ahead of print. PMID: 33460566. Full Text

Dermatology
Olds H, **Liu J**, **Luk K**, **Lim HW**, **Ozog D**, and **Rambhatla PV**. Telogen effluvium associated with COVID-19 infection. *Dermatol Ther* 2021; Epub ahead of print. PMID: 33405302. Full Text

Diagnostic Radiology
Lee EH, Zheng J, Colak E, Mohammadzadeh M, Houshmand G, **Bevins N**, Kitamura F, Altinmakas E, Reis EP, Kim JK, Klochko C, Han M, Moradian S, Mohammadzadeh A, Sharifian H, Hashemi H, Firouznia K, Ghanaati H, Gity M, Doğan H, Salehinejad H, Alves H, Seekins J, Abdala N, Atasoy Ç, Pouraliakbar H, Maleki M, Wong SS, and Yeom KW. Deep COVID DeteCT: an international experience on COVID-19 lung detection and prognosis using chest CT. *NPJ Digit Med* 2021; 4(1):11. PMID: 33514852. Full Text

Diagnostic Radiology
Memon AB, Al-Hader R, Patel S, Malik S, Megally M, Steijlen KL, Suri RR, and **Corrigan J**. Late-onset rapidly progressive MRI- negative-myelitis after COVID-19 illness. *Clin Neurol Neurosurg* 2021; 202:106513. PMID: 33517162. Full Text

Emergency Medicine
Khaldun JS. Public Health Leadership During a Pandemic: Michigan's Experience. *J Public Health Manag Pract* 2021; 27 Suppl 1, COVID-19 and Public Health: Looking Back, Moving Forward:S14-s18. PMID: 33239559. Full Text

Gastroenterology
Mishra K, **Naffouj S**, **Gorgis S**, **Ibrahim H**, **Gill S**, **Fadel R**, **Chatfield A**, **Tang A**, and **Salgia R**. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. *Hepatol Commun* 2021; 5(1):24-32. PMID: 33437898. Full Text

Global Health Initiative
Lucien MAB, Canarie MF, Kilgore PE, Jean-Denis G, Fénélon N, Pierre M, Cerpa M, Joseph GA, **Maki G**, **Zervos MJ**, Dely P, Boncy J, Sati H, Rio AD, and Ramon-Pardo P. Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings. *Int J Infect Dis* 2021; 104:250-254. PMID: 33434666. Full Text

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VasanthiDharmalingam P, Karuppagounder V, Watanabe K, Karmouty-Quintana H, **Palaniyandi SS**, Guha A, and Thandavarayan RA. SARS-CoV-2-mediated hyperferritinemia and cardiac arrest: preliminary insights. *Drug Discov Today* 2021; Epub ahead of print. PMID: 33493677. Full Text

Infectious Diseases
Quan D, Luna Wong L, **Shallal A**, Madan R, Hamdan A, Ahdi H, Daneshvar A, Mahajan M, Nasereldin M, **Van Harn M**, Opara IN, and **Zervos M**. Impact of Race and Socioeconomic Status on Outcomes in Patients Hospitalized with COVID-19. *J Gen Intern Med* 2021; Epub ahead of print. PMID: 33506402. Full Text

Internal Medicine
Mishra K, **Naffouj S**, **Gorgis S**, **Ibrahim H**, **Gill S**, **Fadel R**, **Chatfield A**, **Tang A**, and **Salgia R**. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. *Hepatol Commun* 2021; 5(1):24-32. PMID: 33437898. Full Text

Neurology
Memon AB, Al-Hader R, Patel S, Malik S, Megally M, Steijlen KL, Suri RR, and **Corrigan J**. Late-onset rapidly progressive MRI- negative-myelitis after COVID-19 illness. *Clin Neurol Neurosurg* 2021; 202:106513. PMID: 33517162. Full Text

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Darrat I, **Tam S**, **Boulis M**, and **Williams AM**. Socioeconomic Disparities in Patient Use of Telehealth During the Coronavirus Disease 2019 Surge. *JAMA Otolaryngol Head Neck Surg* 2021; Epub ahead of print. PMID: 33443539. Full Text

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McGrath E, Dalal D, Smitherman L, Marshall S, Youngman C, **Barone CJ**, Gray H, Rehman N, and Secord E. "Would you like a Flu Shot with your order?" - A COVID-19 Pandemic Drive-Through Response to Address Delayed Pediatric Immunization in Detroit, Michigan. *Infect Control Hosp Epidemiol* 2021; Epub ahead of print. PMID: 33397534. Full Text

Public Health Sciences
Brawner CA, **Ehrman JK**, **Bole S**, **Kerrigan DJ**, **Parikh SS**, **Lewis BK**, **Gindi RM**, **Keteyian C**, **Abdul-Nour K**, and **Keteyian SJ**. Inverse Relationship of Maximal Exercise Capacity to Hospitalization Secondary to Coronavirus Disease 2019. *Mayo Clin Proc* 2021; 96(1):32-39. PMID: 33413833. Full Text

Public Health Sciences
Cassidy-Bushrow AE, **Baseer M**, **Kippen K**, **Levin AM**, **Li J**, **Loveless I**, **Poisson LM**, **Schultz L**, **Wegienka G**, **Zhou Y**, and **Johnson CC**. Social distancing during the COVID-19 pandemic: quantifying

the practice in Michigan - a "hotspot state" early in the pandemic - using a volunteer-based online survey. *BMC Public Health* 2021; 21(1):245. PMID: 33514350. Full Text

Public Health Sciences
Mishra K, **Naffouj S**, **Gorgis S**, **Ibrahim H**, **Gill S**, **Fadel R**, **Chatfield A**, **Tang A**, and **Salgia R**. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. *Hepatol Commun* 2021; 5(1):24-32. PMID: 33437898. Full Text

Public Health Sciences
Quan D, Luna Wong L, **Shallal A**, Madan R, Hamdan A, Ahdi H, Daneshvar A, Mahajan M, Nasereldin M, **Van Harn M**, Opara IN, and **Zervos M**. Impact of Race and Socioeconomic Status on Outcomes in Patients Hospitalized with COVID-19. *J Gen Intern Med* 2021; Epub ahead of print. PMID: 33506402. Full Text

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Mouawad NJ, **Lin JC**, Coleman DM, Simmons J, **Kabbani LS**, Cuff RF, and Mansour MA. The initial experience and response of vascular surgeons in Michigan during the COVID-19 pandemic. *Vascular* 2021; Epub ahead of print. PMID: 33504279. Full Text

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Olds H, **Liu J**, **Luk K**, **Lim HW**, **Ozog D**, and **Rambhatla PV**. Telogen effluvium associated with COVID-19 infection. *Dermatol Ther* 2021; Epub ahead of print. PMID: 33405302. Full Text

Urology
Rambhatla A, Bronkema CJ, Corsi N, Keeley J, **Sood A**, Affas Z, **Dabaja AA**, **Rogers CG**, **Liroff SA**, and **Abdollah F**. COVID-19 Infection in Men on Testosterone Replacement Therapy. *J Sex Med* 2021; 18(1):215-218. PMID: 33191186. Full Text